DOCTORAL THESIS

The design and delivery of a patient informed intervention to improve adherence to a gluten free diet in adults with coeliac disease

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The Design and Delivery of a Patient Informed Intervention

to

Improve Adherence to a Gluten Free Diet in Adults

with

Coeliac Disease

by

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When wheat is green, when hawthorn buds appear.

Sickness is catching: O, were favour so…

(Midsummer Night's Dream 1.1. 185-186)

Abstract

The Design and Delivery of a Patient Informed Intervention to Improve Adherence to a Gluten Free Diet in Adults with Coeliac Disease

Coeliac Disease (CD) affects 1% of the UK population, with no cure, the only available treatment is strict adherence to a Gluten Free diet (GFD). It is estimated that 53% to 76% of patients are not adherent to a GFD and this may lead to variety of health related complications. The PhD comprised of three studies; 1, a quantitative exploration of dietary adherence and demographics of CD followed by 2, qualitative interviews to explore patients view in the design of an intervention to increase adherence to a GFD and 3, the design, delivery and evaluation of the intervention.

PhD Aims

To collect information about adherence to a GFD, causes behind low adherence in a mixed cohort of adults diagnosed with CD.

Explore patient preference for a healthcare professional led intervention to promote gluten free dietary adherence in patients with coeliac disease.

Evaluate telephonic clinic intervention in increasing adherence to a gluten free diet in patients with CD, not adhering to the GFD.

Methods

Patients diagnosed with histology confirmed CD were invited to participate. Study I, 375 adults with CD provided cross sectional data collected using validated CDAT and Butterworth questionnaires. Study II, patients with coeliac disease engaged in individual qualitative telephone interview to explore the acceptability interventions to promote GF dietary adherence. Study III, 125 patients (non-adherent intervention group =30) with CD completed baseline CDAT, DASS, CDQoL, GF knowledge questionnaires. The non-adherent group took part in a 1 hour telephonic clinic inclusive of CD and GFD knowledge and behaviour change. Both groups were followed up at three and six months.

Results:

In Study I Gluten free dietary adherence, CDAT score ranged from 7 to 30 with 61% of patients adhering to a GFD. There were no significant differences between GFD adherence based on ethnicity, age, nor gender. Membership of Coeliac UK, affordability of gluten free foods and understanding food labelling were significant factors in GFD adherence. In study II, Caucasians (n=28) and South Asians (n=9) (M=8,

F=29) were interviewed, 30 were considered non-adherent to the GFD. Participants perceived telephone clinics as easy, flexible and convenient, it was the most favoured intervention. Thereafter, in study III, there was a significant improvement in GFD adherence, evidenced by change in CDAT score in non-adherent intervention group (n=30) at three (13.20±1.6) and six months (13.23±1.6) post intervention compared with baseline values (15.7± 0.83, $p<0.01$). Significant increase in knowledge score at three month post intervention (15.07±1.17) was also observed as compared to baseline (13.27±1.48, $p<0.01$), whereas health related QoL remained similar.

Discussion and conclusion:

Patient dietary adherence was 60% in study I as defined by no gluten (except inadvertent intake), is close to the reported value (62%) by Butterworth et al (2004). The study was graded as one of the strongest evidence by the government of UK in relation to consultation prescription of gluten free diet and cited in several recent papers. Study II has given a unique view of a multi-ethnic population to inform interventions aimed at increasing adherence to a GFD. Study III indicates that telephonic intervention can increase in both adherence as well as knowledge scores in adults with coeliac disease who were not adhering to the GFD. Data from this PhD has influenced government prescribing consultation and offers a viable healthcare professional led intervention for clinicians and dietitians.

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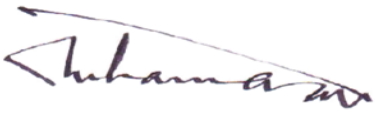
Dedication

This PhD is dedicated to my uncle, Mr Muhammad Zada, a great teacher and a friend who has always been a source of inspiration for me.

Declaration and conflict of interest

This dissertation, and the research contained within, is the work of Dr Humayun Muhammad and other colleagues who have helped in data collection, patient enrolment and design of the study. Although mainly a self-funded PhD, it was partly funded (Study III) by Dr Schär UK Ltd, through their monitory award which was used for stationary and conference attendance.



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Acronyms:

BMD	Bone Mineral density	**GFF**	Gluten Free Food(s)
BSG	British Society of Gastroenterology	**GFP**	Gluten Free Product(s)
CBITP	Computer Based Intervention Programme	**GI**	Gastro Intestinal
CCG	Clinical Commissioning Group	**HRQoL**	Health Related Quality of Life
CD	Coeliac Disease	**IBD**	Inflammatory Bowel Disease
CDAT	Coeliac Disease Activity Test	**IBS**	Irritable Bowel Disease
CDQoL	Coeliac Disease Quality of Life	**IDA**	Iron Deficiency Anaemia
CSI	Coeliac Symptom Index	**IgA**	Immunoglobulin A
DH	Dermatitis herpetiformis	**IL-15**	Interleukin -15
EATL	Enteropathy Associated T-Cells Lymphoma	**NICE**	National Institute of Clinical Excellence
IEL	Intra Epithelial Lymphocyte	**RCD**	Randomised Controlled trial
EMA	Endomysial Antibodies	**SA**	South Asian(s)
FDA	Federal Drug Authority	**T1DM**	Type 1 Diabetes Mellitus
FSA	Food Standard agency	**TTG**	Tissue Transglutaminase
GF	Gluten Free	**UJ**	Ulcerative Jejunitis
GCF	Gluten Containing Food	**VA**	Villous Atrophy
GFD	Gluten Free Diet	**WHO**	World Health Organisation

Publications, communication and presentations associated with this PhD

1: Publications

H Muhammad, S. Reeves, S Ishaq, J Mayberry YM Jeanes. Adherence to a gluten free diet is associated with receiving gluten free foods on prescription and understanding food labelling." *Nutrients* 9.7 (2017): 705.

Y Jeanes, H Muhammad and S Reeves. Improving Gluten-free dietary adherence in patients with Coeliac Disease. Complete Nutrition. Vol.18 No.3 Jul/Aug 2018

Muhammad, H., Reeves, S., & Jeanes, Y. (n.d.). Identifying and improving adherence to the gluten-free diet in people with coeliac disease. Proceedings of the Nutrition Society, 1-8. doi:10.1017/S002966511800277X

Muhammad, H., Reeves, S., & Jeanes, Y. Review of interventions to increase adherence to a gluten free diet in patients diagnosed with coelaic disease. Manuscript under preparation

H Muhammad, S. Reeves, S Ishaq, J Mayberry YM Jeanes. Telephonic Intervention to increase adherence to a gluten free diet in patients with coeliac disease. Manuscript under preparation

H Muhammad, S. Reeves, S Ishaq, J Mayberry YM Jeanes. A tale of two cities. Comparing adherence to a GFD in coeliac disease in two UK cities. Manuscript under preparation

2: Communication to Journal (BSG)

Reeves S, Muhammad H, Jeans Y. Long term gluten consumption in adults without celiac disease and risk of coronary heart disease: prospective cohort study. BMJ 2017; 357 doi: https://doi.org/10.1136/bmj.j1892 (Published 02 May 2017). Cite this as: BMJ 2017;357:j1892.

3: Abstract/ Poster Publications

H. Muhammad, S.Reeves , S Ishaq, J Mayberry and Y.Jeanes. Adherence to a gluten free diet in Caucasians and South Asians with coeliac disease, using the coeliac disease activity test (CDAT) score. The gluten-free die. Coeliac UK conference, Royal College of Physicians, Regent's Park, London. Friday 24 March, 2017. https://www.coeliac.org.uk/document-library/4302-delegates-brochure-2017/?return=/campaigns-and-research/our-research-conference/research-conference-2017

H Muhammad, S.Reeves , S Ishaq, J Mayberry and Y.Jeanes. "PWE-100 Challenges in adhering to a gluten free diet in different ethnic groups." (2018): A168-A168. https://gut.bmj.com/content/67/Suppl_1/A168.1

H. Muhammad, S.Reeves , S Ishaq, J Mayberry and Y.Jeanes. Adherence to a gluten free diet in Caucasians and South Asians with coeliac disease, using the coeliac disease adherence test (CDAT) score. Nutrition Society annual Meeting July 2018.

H. Muhammad, S.Reeves , S Ishaq, J Mayberry and Y.Jeanes. A Tale of Two Cities: Comparing adherence to a gluten free diet in patients with coeliac disease with regular dietitian follow-up from two British cities. 35th Pakistani Society of Gastroenterology meeting 2019.

H. Muhammad, S.Reeves , S Ishaq, J Mayberry and Y.Jeanes. Qualitative interviews to explore patient preference for healthcare led interventions. Coeliac UK conference, Royal College of Physicians, Regent's Park, London. Friday 29 March, 2019. https://www.coeliac.org.uk/document-library/5729-research-conference-2019-posters-11-20/?return=/campaigns-and-research/our-research-conference/research-conference-2019/

H. Muhammad, S.Reeves , S Ishaq, J Mayberry and Y.Jeanes. Intervention improves knowledge of gluten-free foods and dietary adherence in adults with coeliac disease. 13th European National Conference. FENS Dublin. 15-18th October, 2019 (Submitted).

4; Presentations

Coeliac Disease Management and Research. Gastroenterology Specialist trainee Day Teaching. Harrogate District Hospital, 10th June, 2015.

Coeliac Disease research project: Improving compliance in Coeliac Disease. Roehampton University, London. 10th June, 2016

An intervention to improve adherence to the gluten free diet (GFD) in people with coeliac disease. National Dietetic Gastroenterology Symposium. Sheffield 12th may, 2017.

Gluten free diet in people with coeliac disease: identifying and improving adherence in South Asians and Caucasians, a comprehensive approach. Nutrition Society annual Meeting, Leeds July 2018.

5: MSc Dissertations Associated

Alves, Elizabeth. Level of compliance with a gluten free diet and nutritional status of adult's patients with coeliac disease. MS thesis. 2015. (Supervisor Dr Y Jeanes, University of Roehampton)

Townsend H, Jeanes Y. An Investigation into the Micronutrient Adequacy of the Gluten Free Diet as Consumed by those with Coeliac Disease August 2015. (Supervisor Dr Y Jeanes, University of Roehampton)

6: Effect on policies in relation to coelaic disease

Publication associated with this study **(Muhammad et al., 2017)** was presented as a strongest evidence in the UK government's consultation exercise on prescription of gluten free products to patients (2018)." Prescribing Gluten-Free Foods in Primary Care: Guidance for CCG" https://www.england.nhs.uk/wp-content/uploads/2018/11/prescribing-gluten-free-foods-primary-care-guidance-for-ccgs.pdf

7: Awards/ Shortlisting

Dr Schär **Nutrition Project Award 2016. 8000 GBP**. An intervention to improve adherence to the gluten free diet (GFD) in people with coeliac disease. http://www.drschaer-institute.com/uk/news/product-news/winner-of-the-dr-schaer-nutrition-project-award-2016-4593.html

CN award 2015: **Coeliac Professional of the Year shortlisted**. Improving compliance in coeliac disease. http://www.nutrition2me.com/images/awards-uploads/CNAwards2015-Shortlist-Web-070515.pdf

The Nutrition Society (2018): **Winners of the Summer Postgraduate Competition**. Gluten free diet in people with coeliac disease: identifying and improving adherence in South Asians and Caucasians, a comprehensive approach https://www.nutritionsociety.org/node/393/postgraduate-competition

Chapter one

SECTION I

Introduction

Coeliac disease (CD) is a T cell-mediated chronic autoimmune disorder characterised by permanent intolerance to gluten (Shan et al., 2002) in genetically predisposed individuals (Megiorni & Pizzuti, 2012). Gluten is a protein composite found in wheat, rye, barley and related plant species (Farrell & Kelly, 2002). Histologically, CD is characterised by villous atrophy (VA) of the small bowel mucosa (SBM) (Marsh, 1990), which leads to malabsorption of micronutrients (Di Sabatino & Corazza, 2009, Reilly et al., 2012) and when symptomatic leads to diarrhoea, weight loss and abdominal pain (Rampertab et al., 2006). In the majority of cases the condition responds to a gluten-free diet (GFD) (Rubio-Tapia et al., 2010), only to relapse after reintroduction of gluten into the diet (Silvester & Rashid, 2007, Jacobsson et al., 2012). CD has several synonyms: gluten-sensitive enteropathy (O'Grady et al., 1984), coeliac sprue (Austin & Dobbins, 1988), coeliac syndrome (Pink & Creamer, 1967) and non-tropical sprue (Cooke & Smith, 1966). Likewise, there are many other regional names; for example, it is known as *la maladie cœliaque* in French (Malamut, 2012) or *Zöliakie* in German (Holtmeier, 2005), but the term 'coeliac disease', which is also spelled as "celiac disease", will be used extensively in this document, as it is widely recognised and understood in Europe, the United States and the rest of the English-speaking world.

The clinical presentation of CD is variable and based on the presence or absence of symptoms (West et al., 2007). Additionally, CD is a multi-system disorder (Kochhar et al., 2016) and apart from damage to the SBM, it may also affect other organs such as the skin (Collin et al., 2017), bone (Bianchi & Bardella, 2008), liver (Duggan & Duggan, 2005), thyroid (Metso et al., 2012), pancreas (Leeds et al., 2007), nervous system (Cicarelli et al., 2003) and heart (Emilsson et al., 2013). Being a multisystem disorder, physicians should remain vigilant about the long-term complications of CD, which might include osteoporosis (Meyer et al., 2001), anaemia (Mahadev et al., 2018) and more serious complications such as intestinal lymphoma (Catassi et al., 2005).

A GFD is the only practical and successful treatment currently available (Herman et al., 2012, McAllister et al., 2018, Rostami et al., 2017), but adherence to a GFD is extremely challenging (Zarkadas et al.,

2013, Zarkadas et al., 2006) and several published studies estimated the adherence rate to range from 53% to 76% (Hall et al., 2013, Villafuerte-Galvez et al., 2015, Casellas et al., 2015, Rajpoot et al., 2015, Sainsbury et al., 2018).

A GFD is difficult to follow (Olsson et al., 2008) and many patients refer to the social and practical issues in regard to following a strict GFD (Hall et al., 2009). Based on studies to date, there is limited available information on factors affecting adherence with a GFD (Errichiello et al., 2010, Villafuerte-Galvez et al., 2015, Halmos, Deng et al., 2018); for this reason regular follow-ups in specialised CD clinics are advised to monitor adherence, provide appropriate support and take necessary actions in case of dietary transgressions (Pietzak, 2005), as this may improve and maintain adherence to a GFD (Rajpoot et al., 2015).

The literature review will focus on the definition of CD, followed by a brief historical perspective and related epidemiology, as well as an overview of the background pathology. The clinical features of CD will then be narrated briefly, followed by a detailed discussion on adherence to a GFD and possible causes and interventions to improve such adherence in CD patients.

Definition and historical account of Coeliac Disease

Earlier attempts to define CD mainly concentrated on clinical and histological aspects, being defined by Meeuwisse (1970) as:

'A permanent condition of gluten intolerance with mucosal flattening that reversed on a gluten-free diet (GFD) and then relapsed on re-introduction of gluten.'

This definition has noticeably taken into account the histological appearance of CD and the entire definition hinges upon abnormal SBM after exposure to gluten. Over time, as research has explored clinical, histological, epidemiological and then genetic aspects of the disease, the definition of CD has evolved as well (Walker-Smith et al., 1990). In search of a holistic definition, several years ago Ludvigsson et al (2013b), after evaluation of a number of studies (n=300), proposed a new consensus definition termed the 'Oslo definition'. This conclusive definition took into account various deficiencies previous definitions had, and these were addressed in the light of modern research. CD according to this definition is:

'A chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals' (Ludvigson et al., 2013).

This definition is simple and encompasses different levels of CD: namely dietary aetiology, pathology and genetic predisposition. Moreover, the definition was proposed by a multidisciplinary task force of 16 expert physicians from seven countries, after a thorough search of the electronic database involving group discussion, web surveys, consensus statements and detailed feedback. As a result, the definition makes the terminology clearer and the basic purpose of developing this definition was to validate terms in relation to CD and aid in clinical management and future research. The table below shows the changes in terminology in relation to CD (Table No 1).

Table 1: Novel terms in the Oslo definition along with discarded terms. Modified from Leonard & Vasagar (2014).

Suggested Terms	Characteristics	Related terms out of favour
Classical CD	Signs and symptoms of malabsorption; e.g. diarrhoea and poor growth.	Typical CD
Non-classical CD	Symptoms other than malabsorption	Atypical CD
Subclinical CD	Clinical and laboratory signs of CD without symptoms sufficient to suggest testing	Asymptomatic/ Silent CD
Symptomatic CD	GI or extra-intestinal symptoms occurring due to gluten ingestion	Overt CD
Potential CD	Positive serological testing with normal small bowel biopsy	Latent CD
Refractory CD	Persistent symptoms and enteropathy despite strict GFD for more than 12 months	

There is however some criticism of the definition and researchers have pointed out the lack of novelty in the definition or an evidence based consensus in the development of the definition (Di Sabatino & Corazza, 2013, Mäki, 2012). However, following the publication of this definition, it appeared in numerous (n=960) review articles and studies (Czaja-Bulsa, 2015, Marsh, 2013, Kocsis et al., 2013, Kenrick & Day, 2014) and has been cited by the British Society of Gastroenterology (BSG) in their up-to-date guidelines on CD (Ludvigsson et al., 2014b). It is felt that, despite these observations, the definition *per se* is practical, the process to adapt the definition was methodologically sound and equally there is no study to prove its triviality, hence this definition will be referred to in this document.

Historical perspective of Coeliac Disease

CD was first described by Aretaeus of Cappadocia (present-day Turkey) in 250 AD (TekıNer, 2015). He referred to the condition as 'koiliakos' (κοιλιακός), i.e. to do with the bowels or abdomen, although, prior to this, intestinal disease and malabsorption was referred to in 15 BC Indian literature (Bures, 2018). The term came to English as 'coeliac' with Francis Adams' translation of these observations from Greek to English (Adams, 1856). The dietary link with CD was first described in 1888 by Samuel Gee, a British physician, in his book "*On the Coeliac Affection"* (Gee & Gibbons, 1939). Initially, it was postulated that

a toxic component in the diet was responsible for the disease, yet no such component was identified over the next 70 years, despite multiple attempts (Losowsky, 2008, Booth, 1989).

The final breakthrough came during World War II, following vigilant observations made by Dutch paediatrician Willem Karel Dicke on a cohort of young children suffering from chronic diarrhoea and weight loss (Dicke, 1941). One famous account describes how, when the Nazi regime blocked supply routes, cereals to make bread were in extreme shortage and were replaced with non-wheat containing alternatives. This subsequently led to symptomatic improvement and Dicke became convinced that it was the absence of wheat-related products that brought about improvements in the symptoms of CD (Dicke, 1950). Principal historical developments are shown in the chart below (Fig No 1).

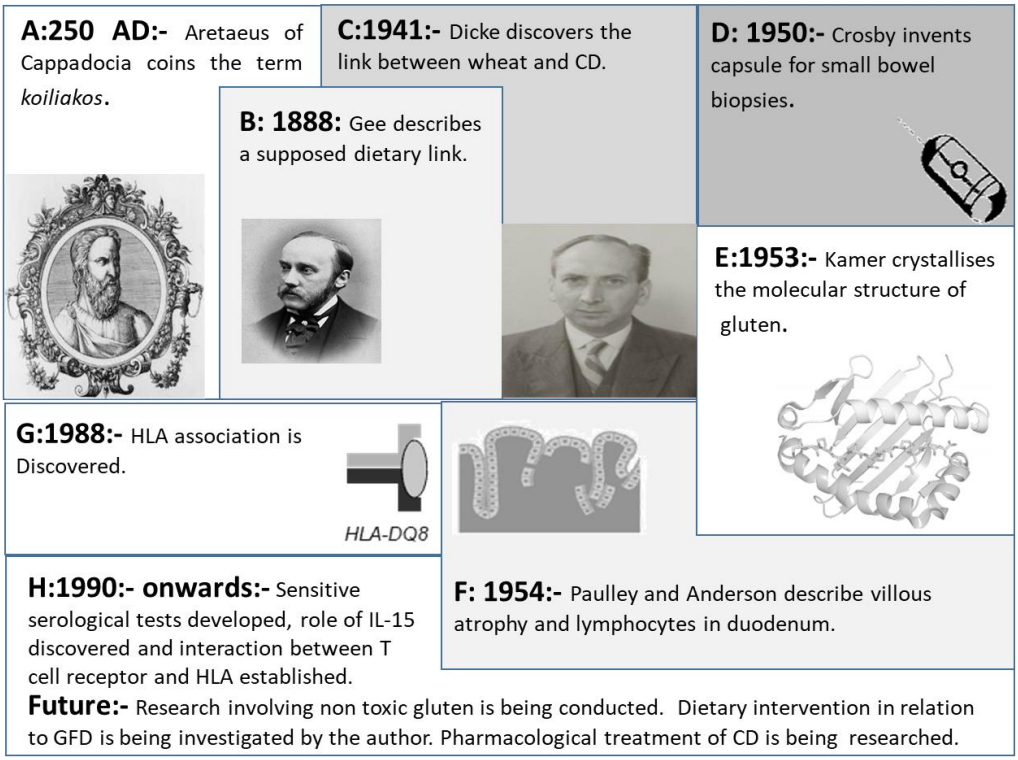

Figure 1: Principal historical developments in relation to CD.

Over the past 25 years, insight into CD has undergone major development and new information has emerged about its epidemiology, patho-physiology, diagnostics and management. Indeed, the key patho-physiological steps and role of tissue transglutaminase (tTG) in relation to CD have been discovered (Molberg et al., 1998). At the dawn of the new century, clinico-pathological understanding further increased and enteropathy-associated T cell lymphoma (EATL) was described (Cellier et al.,

2000b). Similarly, non-dietary treatments (Schuppan & Junker, 2007) and the role of IL-15 (Mention et al., 2003) were also explored. At the molecular level, the structural interaction between T-cell receptor (TCR) HLA and tissue glutaminase has been the subject of recent research (Petersen et al., 2014, Chen et al., 2015). In addition, novel methods of intervention have been proposed by researchers to increase adherence with a GFD (Sainsbury, Mullan & Sharpe, 2013b). Very recently, sensitive urine tests have been developed to detect Gluten Immunogenic Peptides (GIP) in patients not adhering to a GFD (Moreno et al., 2017). Nonetheless, one of the key issues still needing to be addressed is the development of a cost-effective, patient-friendly, widely accessible and effective therapeutic strategy that will increase adherence to a GFD.

Pathology and pathogenesis of Coeliac Disease

CD is one of the classic examples where a number of genetic, environmental and immune factors interact and give rise to disease of varying degrees of severity, as it is the close interaction between an environmental agent and a host with appropriate genes that allows it to develop.

Role of genetic predisposition in Coeliac Disease

Among these factors, genes are non-modifiable and have long been known to cause CD (Corazza et al., 1992). The intra-familial occurrence of CD and concordance rates for CD in monozygotic twins (as suggested by family studies) show that genetic factors are important causative agents in CD pathogenesis (Schmitz, 1997, Ellis, 1981, Wijmenga & Gutierrez-Achury, 2014). Moreover, research in the area of genetic linkage shows that CD has a strong association with HLA-DQ genes and patients who carry DQ2 or DQ8 alleles (Karell et al., 2003). Almost all patients with CD carry a subtype HLA-DQ8, which means that if this haplotype is not present, the likelihood of CD is very rare. In other words, this has a negative predictive value in the diagnosis of CD (Lebwohl et al., 2014b) and helps in the exclusion of CD in equivocal cases (Kaukinen et al., 2002a). Yet, this notion might not be universally true, as suggested by a Spanish systematic review, which found 3% of HLA negative patient were later diagnosed with CD (Fernandez-Banares et al., 2017). The exact clinical significance of this finding is not clear.

Allied to this concept, the genetics of CD have been studied in Indian patients and were found to be related to the same HLA alleles as in Western Europeans (Amarapurkar et al., 2016), but this is an under-researched area that few studies have explored (Agrawal et al., 2000, Kaur et al., 2002, Shanmugalakshmi et al., 2003, Senapati et al., 2015). It is therefore considered that this area is in need of further research.

Role of gluten in the pathogenesis of Coeliac Disease

The most established and modifiable factor is the environmental agent for CD, which is found in wheat protein. Wheat (*Triticum aestivum*) itself comes from the family of grains that is divided into two groups, namely Festucoideae and Panicoideae. The former is further divided into three tribes and wheat belongs to the Triticeae tribe along with rye and barley (Kasarda et al., 1984). Oats belong to a related tribe and it is this taxonomic remoteness that makes oats relatively safe for consumption in CD (Cooper et al., 2013). Correspondingly, rice, corn, sorghum and millet – although grains – are taxonomically different

from wheat and are thus safe to consume in CD. The taxonomic relationship of the wheat family is shown in the figure below (Fig No 2).

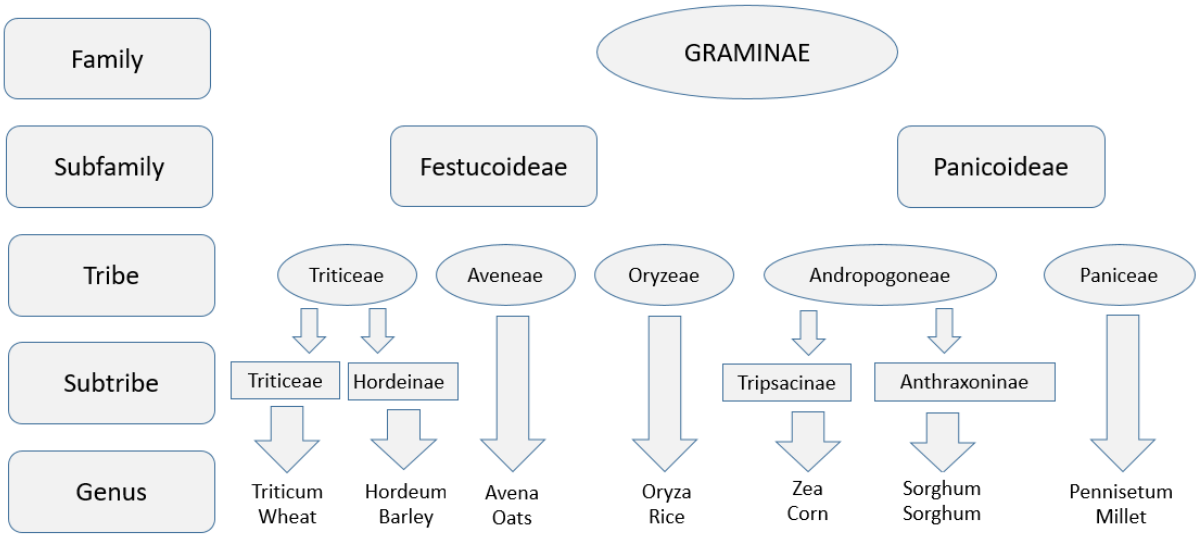

Figure 2: Taxonomic relationship of the major cereal grains. Modified and redrawn from Sleisenger's gastroenterology (Feldman et al., 2015).

Wheat proteins are classified on the basis of their solubility characteristics and fall into four general groups: prolamins, glutenins, globulins and minor albumins (which are soluble in alcohol, dilute acid, normal saline and water respectively) (Feldman et al., 2015, DuPont et al., 2005). Gluten is a combined term for both prolamin and glutenin (Biesiekierski, 2017). Although most studies performed suggest that prolamin is the toxic component, there is also evidence to suggest that glutenins can be toxic in this context (De Vincenzi et al., 1996). Gluten from wheat is known as gliaden, as opposed to gluten from rye (secalin) and barley (hordein). Electro-physiologically, gliadin can be separated into four fractions (α-, β-, γ-, ω- gliadins) (Ciclitira & Ellis, 1987). Gluten is capable of activating T cells to generate lymphocytic inflammation (Vader et al., 2002).

Role of the immune system in CD

Both humoral and cellular immune responses directed against polyamines play a major role in the pathogenesis of CD, as shown by the substantial recruitment of B cells in the lamina propria of the small intestine and presence of antibodies to gliaden in the sera of patients with active CD (Troncone & Discepolo, 2014, Lindfors et al., 2010). The target autoantigen here is tTG. There is evidence to suggest that interleukin subtype 15 (IL-15) plays a major role in the pathogenesis of CD and it is both cytotoxic

as well as a recruiter of other inflammatory cells (Maiuri et al., 2003). These events are summarised in the figure below (Fig No 3).

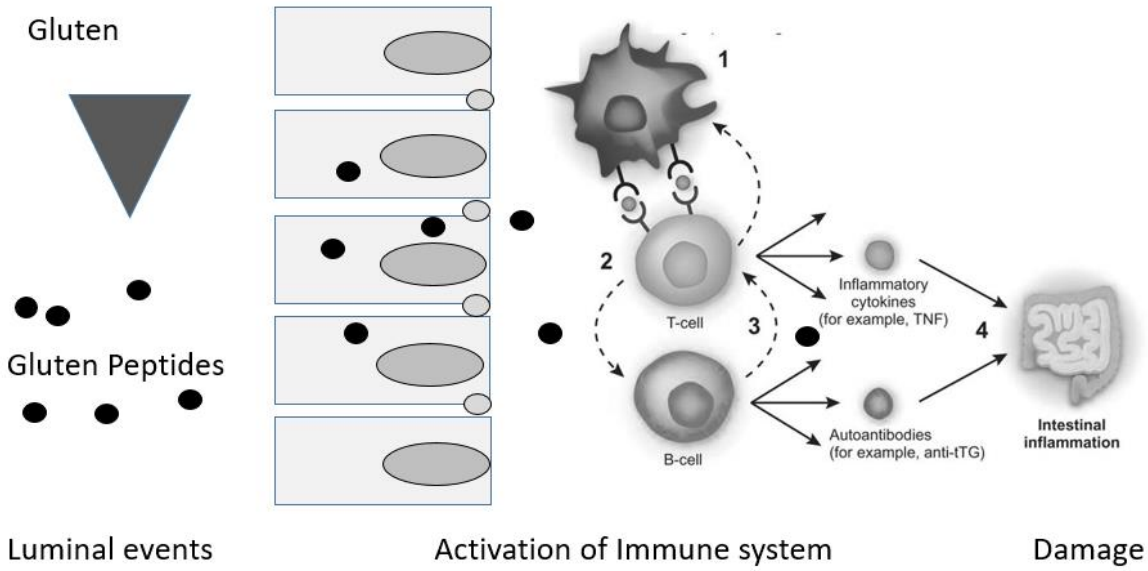

Figure 3: Pathogenesis of CD: 1: Antigen presentation 2: Activation of T cells 3: Immune interplay between T and B cells 4: Inflammation in small intestine. Modified and redrawn from (Kagnoff, 2005, Plenge, 2010).

The proposed sequence of events is: luminal breakdown of gluten which releases the toxic gluten peptides; these are taken up by the luminal cells and absorbed; antigen presenting cells process these peptides, leading to the activation of both T (Jabri & Sollid, 2017) and B cells (Hietikko et al., 2018); this leads to inflammation of the intestinal mucosa. On gross examination, the duodenum may appear "scalloped" (Oxentenko et al., 2002) and the histology shows characteristic VA as standardised by Marsh and Crowe (1995) and latter modified by other researcher (Antonioli, 2003, Das et al., 2019). A detailed discussion of these histopathological findings is beyond the scope of this work, but a summary of these histopathological findings is shown below (Table No 2).

Table 2: Modified Marsh Classification. Adapted from Antonioli (2003).

Type	IEL/100 EI D	IEL/100 EI J	CH	Villi
0	<40	<30	Normal	Normal
1	>40	>30	Normal	Normal
2	>40	>30	Increased	Normal
2a	>40	>30	Increased	Mild atrophy
3b	>40	>30	Increased	Marked atrophy
3c	>40	>30	Increased	Complete atrophy

Abbreviations/ explanation: IEL/ 100 enterocytes (E) intraepithelial lymphocytes (I) per 100 enterocytes, duodenum (D), Jejunum (J), cryptic hyperplasia (CH). Severity: Normal to increasing 0 -3c.

Additionally, there may be other confounders affecting the expression of the disease, because this simple model does not explain all the clinical behaviours of CD. The protective effect of breast feeding was referred to in the literature as early as 1983 (Ivarsson et al., 2002) and later a meta-analysis (Akobeng et al., 2006) of carefully selected studies (n=6) examined the risk of CD and reported that it was significantly increased in infants who were fed gluten at the time of breast feeding, as compared to those who were not (pooled odds ratio 0.48, 95% CI 0.40 to 0.59). Subsequently, a large two phased cross sectional screening study (n=13279) reported the protective effect of prolonged breast feeding and suggested a gradual introduction of gluten into the diet when weaning (Ivarsson et al., 2013).

Similarly, two prospective cohort studies examined the duration of breastfeeding and time of introduction of gluten into the diet and found that longer duration of breastfeeding (Lionetti et al., 2012) and late introduction of gluten may offer protection against CD (Aronsson et al., 2016), but a later systematic review did not give clear guidance about the duration of breastfeeding as such (Silano et al., 2016). It is thus concluded that early introduction of gluten and early weaning do play some role in the causation of CD and gradual introduction of gluten is favourable. However, the exact mechanism is not clear and more research is needed in this area.

Rotavirus infection has been found to cause CD in genetically predisposed individuals, as suggested by a prospective cohort study (Stene et al., 2006). This longitudinal study (n=1931) involved infants who were genetically susceptible to CD at birth on account of their HLA and were followed up with serological tests for CD and Rotavirus. However, the diagnosis of Rotavirus was not clinical; rather it was based on

serology. In the same year, another study (n=60) examined patients' sera for peptide sequence and this shared a high degree of homology with the Rotavirus, suggesting a possible role in the causation of CD (Zanoni et al., 2006). These findings were further confirmed by the same group in a later study (Dolcino et al., 2013). The same author also implicated the role of Rotavirus in non-coeliac gluten sensitivity in a recent study (Puccetti et al., 2018). These studies are not conclusive, but do point towards the fact that CD may be prevented by avoiding Rotavirus infection; but the oral vaccine developed against Rotavirus did not alter the risk of CD (Vaarala et al., 2017). Additionally, the whole notion of Rotavirus causing CD was questioned by Ziberna and colleagues (2016). It is felt that this is an evolving area and more research is needed here.

There are other factors which may play a role in relation to CD. Cammarota (2000) published a case report where a 42 year old patient with Hepatitis C developed CD after initiation of Interferon treatment: a finding later confirmed by a retrospective case series (Durante-Mangoni et al., 2004). Similarly, another author suggested that there might be an epidemiological link between Hepatitis C and CD (Colombo et al., 2003). Likewise, increased birth weight was yet another factor linked with the causation of CD, in a retrospective Swedish study (Kuja-Halkola et al., 2017). However, the author admits that, when comparing discordant twin pairs in within-twin pair analyses, no significant difference was found, suggesting that high birth weight does not play a definitive role in causing CD. Other factors, such as mode of delivery and maternal antibiotic intake during gestation, were examined in a population cohort study (n=54) and there was some suggestion that antibiotic intake may cause CD (Pozo-Rubio et al., 2013). This study however indirectly inferred the causative role lymphocyte activation, which may or may not be related to the CD. It is thus accepted that genetics alone cannot explain the causation of CD and more research is needed in this area.

Epidemiology of Coeliac Disease

Ethnicity, Sex and Age

Previously, it was thought that CD was primarily a Western European disease that followed the Caucasian race through the route of their migration to the United States and Australia (Johnston et al., 1998). Yet this is not entirely true. With the introduction of sensitive serology, CD is now also being diagnosed in areas where wheat is the main dietary staple, such as the Indian subcontinent, North West and East Africa, the Middle East and South America (Akbari et al., 2006, Dalgic et al., 2011, Bhattacharya et al., 2009, Malekzadeh et al., 2005). Additionally, there are gender differences: research shows that there is a clear female preponderance in the diagnosis of CD, ranging from 60 to 70% of the diagnosed and undiagnosed cases (Bai et al., 2005, Dixit et al., 2014, Shah & Leffler, 2010, Ivarsson et al., 2003, Jansson-Knodell et al., 2018), although there is a suggestion that the difference disappears with advancing age (Fasano et al., 2003). This apparent discrepancy remains unexplained and one may argue that there are gender differences in health-related help-seeking behaviour (Oliver et al., 2005), by the observation that females tend to visit their GP more often (Vedsted & Christensen, 2005, Corney, 1990) than their male counterparts (Galdas et al., 2005). Additionally, anaemia, a presenting sign of CD (Harper et al., 2007), which is common in pregnancy (Goonewardene et al., 2012) and osteoporosis, a commonly reported condition in females (Cawthon, 2011), is associated with CD and may necessitate CD testing, which may then increase the number of diagnosed females cases. A recent meta-analysis looking at data from 87 studies (n= 291,969) showed that the pooled prevalence of CD among females was 0.589% as compared to males (0.415%), with females carrying a higher risk of undetected CD (Jansson-Knodell et al., 2018). However, evidence to explain this gender disparity is insufficient and it appears to be multifactorial in nature and more research is needed to explore this discrepancy between genders.

CD affects all age groups and is not just a paediatric disease. Currently, a quarter of cases are diagnosed in patients aged 60 or above (Vilppula et al., 2009), with a mean age of 45 years (Rubio-Tapia et al., 2012) and rising (Mukherjee et al., 2010). Increasingly, cases of the subclinical disease are being diagnosed, after investigation through case finding of first-degree relatives of CD-affected individuals (Tajuddin et al., 2009). Nonetheless, the general trend identified in the presentation of CD is increasing age at diagnosis, along with a shift from classical to non-classical CD, as suggested by retrospective cohorts spanning more than 55 years (Castro et al., 2017, Whyte & Jenkins, 2013).

Incidence of Coeliac Disease

The incidence of CD has been estimated in several population-based research studies and a wide range between 2-13/100,000 per year is reported, which is multifactorial (Rewers, 2005). A US based study spanning over 50 years has estimated incidence to be 2.1/100,000 per year (Murray et al., 2003a), but this might be marred by diagnostic bias, as sensitive endoscopic and serological tests to diagnose CD have evolved over the past 40 years. Similarly, an extensive review covering the European and Mediterranean region estimates that the incidence ranges from 0.1 to 3.7/1000 live births in the child population and from 1.3 to 39/100,000/year in the adult population (Altobelli et al., 2014). Nonetheless, it is accepted that all adults diagnosed in such studies may not necessarily have been true new cases (incidence), as the condition may well have been subclinical and have been present for decades and hence undetected, which could have falsely inflated the incidence rate (Rewers, 2005).

Two associated phenomena in this regard are the geographic variability of the incidence of CD and rising levels of incidence worldwide. For example, in Europe the incidence of CD is especially high in the Scandinavian (Ivarsson et al., 2000) and Celtic populations (Maki et al., 2003), where the reported incidence is around 3.5 per 1000 live births (Cavell et al., 1992). Genetic factors are not the sole cause for this regional diversity however, as Denmark has an approximate incidence which is 40-fold lower than the Norwegian population (Weile et al., 1995), despite the fact that they share the same gene pool. This notion is further supported by the presence of discordance between monozygotic twins in the expression of CD (Bardella et al., 2000). It is thus accepted that this area needs more research. Secondly, the incidence of CD is on the rise and this has been reported by several studies (Ludvigsson et al., 2014a, Ludvigsson et al., 2013a, Murray et al., 2003b, Canavan et al., 2014), but the exact reason for this rise is not clear and is thought to be multifactorial. The rise in incidence is complex and could be partly attributed to refining the diagnostic criteria and, more importantly, the availability of sensitive serological tests (Lohi et al., 2007); but the design and selection of participants can also affect the incidence of CD. Methodology of the study may play a role, as in the systematic review by Kang et al. (2013), which identified 15 studies that primarily used blood donors when looking at the incidence of CD; it is clear that this will lead to selection bias, as blood donors are less likely to be anaemic (one of the main laboratory findings for CD) (Harper et al., 2007). Additionally, there are a number of studies that point towards environmental factors and regard part of this rise in incidence as a true increase (Ivarsson et al., 2013, Lohi et al., 2007). Industrial usage of gluten is conceivably one such factor leading

to an increase in the incidence of CD (Catassi et al., 2014), but no strong evidence exists to support this notion.

Similarly, other factors like differences in human leukocyte antigen (HLA) or variability in the infant formula at the time when gluten is introduced into the infant's diet might well play a part (Norris et al., 2005). A methodologically superior later study suggested that this increase in the diagnosis may be up to two fold in genetically predisposed children, if gluten is consumed before the age two (Aronsson et al., 2016). It is, however, accepted that it is difficult to give a detailed account of this complex area partly because of its multifactorial nature and the paucity of research in this area.

Incidence of CD has been estimated in the UK as well and there is clear geographical variation. In England, for example, the reported incidence of CD is 8.7/100,000 per year as suggested by histo-pathologically diagnosed cases (Fowell et al., 2006). The study examined all referrals to a gastroenterology department (from 1992 – 2002) and may well have been affected by referral bias. Similarly a Scotland based study estimated incidence to be 11.7/100 000 per year. Yet another non-geographically bound UK based study (West et al., 2014) reported it to be 19.1/100.000 per year and demonstrated a geographical difference between Northern Ireland (22.3) and London (10). It is felt that the latter study is close to the true estimate of incidence, as it is not geographically bound and has accessed a more thorough database instead of relying on referrals in a single department.

Following the general trend, four studies have reported an increase in the incidence of CD in the UK from 1960 to early 2000, with two of them using the same population (Hurley et al., 2012, White et al., 2013, West et al., 2014, Hawkes et al., 2000). It is accepted that a re-analysis of all evidence for UK based studies needs to be done, followed by population based research. It is also accepted that the aetiology of CD is multifactorial and may well explain this rise in incidence. To address this question, however, it is suggested that further research is needed in this area. One possible study design might be the mass screening of a given population followed by similar screening after a quinquennium with longer follow ups.

Prevalence

Reported prevalence of CD (proportion of patients with CD at a given time) ranges from 1:70 to 1:300 in most of the world's populations (Gujral et al., 2012); there is also a suggestion that the prevalence has increased over time (Rubio-Tapia et al., 2009, Riddle et al., 2012). Moreover, variability is seen in different populations, with the reported prevalence being very low in Chinese (Yuan et al., 2017) and

related ethnicities (Cummins & Roberts-Thomson, 2009), whereas those with the highest prevalence of CD (5.1%) are in a North African tribal population (Barada et al., 2010). This remains unexplained and may have an environmental cause such as high gluten intake or the presence of a high carrier rate of HLA type DQ2 and DQ8 genes and more research is needed.

Following global trends, the overall prevalence rate for CD in northern Europe is 1% (Feldman et al., 2015), yet it has long been known that geographic variation exists in the reported prevalence of CD in Europe (Pittschieler & Ladinser, 1996), which ranges from 0.7% to 2.4 % (Mustalahti et al., 2010). Similarly, in the UK, the estimated prevalence for CD ranges from 0.5% to 1% (Ciclitira et al., 2010, Aggarwal et al., 2012, Sanders et al., 2001). The reported variation in population-based studies is determined in part by the design of the study and the diagnostic criteria used, HLA of the subject population and variation in pathological reporting.

Prevalence is dependent on the age of the patient and increases with age, as 25% of adults are diagnosed with CD after the age of 60, as suggested by a recent review (Collin et al., 2018). Similarly, in children for example, the prevalence rate is 1:285 as suggested by a US based study (Fasano et al., 2003). Likewise, an Italian study with substantial power (n=17,201) estimated the prevalence in school-going children (between the ages of 6 and 15) to be 1:184, which means that for each diagnosed individual in Italy there are thought to be seven undiagnosed cases of CD (Catassi et al., 1996). In contrast, the prevalence in adults of positive serology for CD is found to be higher and close to 1:105 (Fasano et al., 2003). Additionally, prevalence for VA is 1:99 (Maki et al., 2003) and for active disease is around 1:1750 (Murray et al., 2003b). Furthermore, the prevalence also varies if other factors are considered, such as patients with type I diabetes and people with affected first-degree relatives, where the prevalence is between 20% and 15% respectively (Dubé et al., 2005).

Prevalence is also dependant on the testing methodology (serology, histology or a combination) used to diagnose CD. In this context, one US-based study (n=13,145) measured prevalence in both the general population and high-risk groups (i.e. close relatives of diagnosed CD patients or symptomatic patients) by both serology and histology. The reported prevalence was 1:22 to 1:56 in at-risk groups and 1:133 in the not at-risk population. It is nonetheless possible that the study missed a number of cases, as serology is not 100% sensitive (Sayed et al., 2012). Globally, studies which measure prevalence using biopsies report prevalence in the range of 1:300 to 1:500 (Fasano, 1996, Størdal et al., 2013, Al-Hussaini et al., 2017), which is more objective in terms of diagnosis.

Notwithstanding the fact that the studies above rely on data available from diagnostic tests, retrospective clinical case findings and questionnaires, true epidemiological indices might not be known, as CD has a protean clinical nature and remains an under-diagnosed or misdiagnosed condition (Lohi et al., 2007). This is because the symptoms are vague, overlap with irritable bowel syndrome (IBS) and may coexist with other similar diseases. For example, a study (n=100) which evaluated the presence of CD in patients presenting with symptoms of IBS (by performing serology and duodenal biopsies) found that 8% of patients had serological as well as histological evidence of CD (Shalaby et al., 2016).

Moreover, the prevalence of asymptomatic CD in the general population is 0.75% (1 in 132), as suggested by a Swedish study (n=1450) examining asymptomatic students, which makes it difficult for asymptomatic individuals to qualify for serological testing if relying on symptoms or reporting to their family doctors; hence they may evade diagnosis. Furthermore, in underdeveloped countries it is assumed that limited access to diagnostic testing may further underestimate the true prevalence, but research studies are needed to test this assumption.

Mass screening may be one solution to detect all cases, but it is not known whether this is the best strategy for both patients and the health system, as a critique by Evans et al., (2009) explained. In addition, there are economic implications for the NHS and this could also affect the quality of life for patients who are asymptomatic but have been diagnosed with CD (Paavola et al., 2012). It may, however, offer early recognition and treatment of the condition and thus reduce the risk of associated malignancy, but a population cohort with longer follow-up is required to make a case for such an intervention.

Being a global disease, in wheat-cultivating regions in particular, CD affects the South East Asian population as well. Over recent decades, South Asians (SA) have migrated in huge numbers to westernised countries in Europe and the Americas (Casanova, 2007). Naturally this means that their genetic predisposition to CD has been taken along with them, as shown by research involving immigrant populations (Walker-Smith, 1973, Sher et al., 1993, Butterworth et al., 2005, Walia et al., 1966, Khoshoo & Bhan, 1989). These studies were primarily population-based cohorts and involved both retrospective and prospective methodologies. Prior to that, it was anecdotally known that when rice was replaced with varieties of wheat-containing grains in summer, the incidence of diarrhoea increased – known as ‘summer diarrhoea’ in the indigenous areas (Sher et al., 1993). Early this century, well-designed prospective epidemiological studies were conducted and one study (n=4347) is particularly worth

mentioning. Children aged 3 to 17 were enrolled in the study and checked for CD (Sood et al., 2006); only 14 were found to have duodenal changes consistent with CD. Thus the reported prevalence of biopsy-proven CD was 1:310. The study, however, may be criticised for the fact that diarrhoea is a common symptom in North India and, due to infectious aetiologies and anti-tTG, cases of CD were conceivably missed; hence adjustment may be needed to interpret the results.

The prevalence of cryptogenic cirrhosis has been reported to be as high as 10% in a subgroup of Indian patients (Maiwall et al., 2014), yet this overestimation can be explained by the fact that CD itself causes chronic liver disease. Considering these pitfalls, three well-designed and high-powered studies reported the prevalence to be close to1% (Bhattacharya et al., 2009, Makharia et al., 2011, R. Kochhar, Sachdev et al., 2012), which is around the value reported in Western literature (Ciclitira et al., 2010, Aggarwal et al., 2012, Sanders et al., 2001). In contrast to North India, CD is considered to be rare in South India (Sathiyasekeran & Shivbalan, 2005, Ramakrishna et al., 2016), although this may be related to under-reporting of the disease (Yachha et al., 2006) and lack of high quality studies (Ramachandran & Jacob, 2016).

The prevalence and clinical presentation of CD are similar in Pakistan and North India (Rashid & Khan, 2009, Z. Abbas et al., 2013). Two studies examined the symptomatic presentation of CD. The first was a retrospective study (n=77) which reported the typical presentation of CD was diarrhoea and it was the presenting symptom in 65% of the patients (Abbas et al., 2013). The second study (n=66) was prospective and reported the main symptom of CD as diarrhoea in half of the patients (Masood & Ali Shaikh, 2014). Reported high frequency and equally high variability of a symptom may be explained by the fact that diarrhoeal illnesses are common in Pakistan due to infectious aetiologies, and it is quite possible that atypical CD patients with infectious diarrhoea have been included in these studies.

Yet another study which examined the paediatric age group (n=66), in a 5 year prospective cohort, reported abdominal distension as the main presenting feature (Aziz et al., 2017). HLA association was also explored in a study which found that HLA-DRB1*03 is associated with CD in Pakistan (Saleem et al., 2013). This case-control study was low powered. It is nonetheless accepted that this area is under-researched in Pakistan and more prospective epidemiological studies with high power are required.

The incidence of CD is increasing on the subcontinent also and one study reported that this situation is in parallel with the Western trend (Sood et al., 2001). Following this, in 2009, the Indian task force for

CD reported that the incidence of CD in India is no different from the rest of the world (Gupta et al., 2009). It is thus considered that the epidemiological characteristics of CD in SA are indistinguishable from the rest of the world's population as suggested by meta-analysis (Singh et al., 2016), although this area still requires high-powered and prospective studies.

Studies examining SA resident in Britain are sparse, but worth noting is a seminal study (n=130) by Butterworth and colleagues (2005) on British Asians, comparing the population with indigenous Caucasians in a case-matched manner. The study reported that prevalence in the Caucasian population and SA was 1:356 and 1:193 respectively ($p<0001$). This significant difference in prevalence was reversed when analysed for age 65 and above. There was no difference in the mean age of presentation between the two groups, which ranged from 34 to 36 years. The study was prospective and low powered.

Similarly, a Leicestershire-based study (n=106) retrospectively examined the incidence of CD in Punjabis and Gujarati population settled in Leicestershire from India/Africa. It was found that they developed the disorder 2.7 times more often than white Europeans (Sher et al., 1993).

Later, a retrospective study (n=1305) found that 0.6% of Asians were diagnosed with CD in the Derbyshire area in the UK (Holmes & Moor, 2012). The study pointed to the previous observation of increased diagnosis of CD among Asians and agreed with Sher and colleagues (1993). Although well designed, the study underestimated the true proportion of CD for SA.

SECTION II

Clinical presentation of Coeliac Disease

The clinical presentation of CD is not straightforward and the initial classical description of CD in the literature, comprising chronic diarrhoea, generalising wasting and severe malnutrition (Plotkin & Isselbacher, 1964) is rare nowadays – especially in the developed world (Dixit et al., 2014, Reilly et al., 2012). Symptoms of CD may not reliably correlate with the degree of inflammation in the SBM (Cronin et al., 2018).This is because CD involves the duodenum in a patchy fashion (Hopper et al., 2008), leading to VA of variable severity, hence variable degrees of malabsorption (Yachha et al., 1993). The critical decrease in small bowel surface area to cause malabsorption may not be achieved in all patients and this may partly explain the variability in clinical presentation of CD (Rampertab et al., 2006). It could best be described as an iceberg model (Admou et al., 2012) based on the presence or absence of symptoms (Fig No 4).

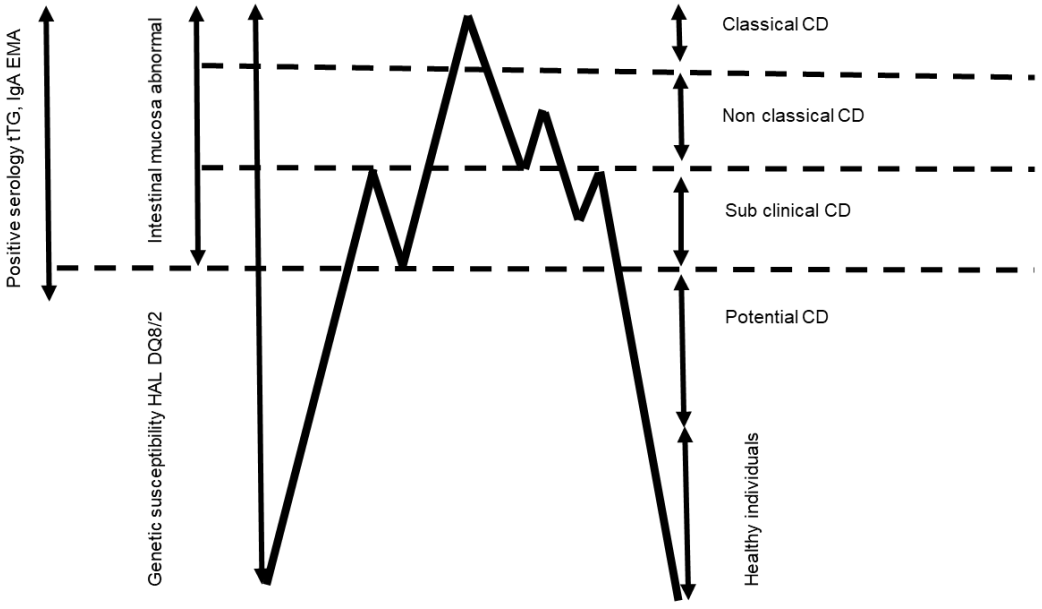

Figure 4: Coeliac Disease iceberg. Modified extensively and redrawn from Sleisenger's gastroenterology (Feldman et al., 2015) **in the light of the Oslo conference (Ludvigsson et al., 2013b).**

The tip of the iceberg displays the symptomatic disease and includes classical CD, which was first described by Gee (1939) and presents with diarrhoea, weight loss and abdominal pain (classic symptoms) with supporting serological and histological evidence (Wahab et al., 2002). This pattern of

presentation is decreasing, as suggested by an extensive Irish study (n=749) examining the health records of CD patients from 1960 to 2015 (Castro et al., 2017). The second type (non-classical CD) presents with no signs or symptoms of malabsorption, although mono or oligo symptoms may be present. These symptoms were reviewed by Admou and colleagues (2012), who enumerated a number of symptoms and laboratory signs such as: anaemia, vomiting, constipation, headache, neuropathy and short stature. This type of CD is often missed in clinical settings because of its protean nature of presentation (Singh & Makharia, 2014). The third type in this group is the submerged portion consisting of subclinical or silent CD, which has fully expressed serology and associated enteropathy but no symptoms; this is the most common type (Rampertab et al., 2006).

The final type in the above figure is potential CD, which has the required HLA and positive serology but does not have abnormal SBM (Sperandeo et al., 2011). A study utilizing MRI to detect a metabolic signature suggests that there is increased metabolic activity on MRI when this group is exposed to gluten (Bernini et al., 2010), but the clinical significance of this study is not clear. Not shown in the iceberg model are two other types of CD, based on the clinical response to a GFD: namely nonresponsive and refractory CD, which will be referred to later in the review. The consensus conference in Oslo (2014) adopted these terms, with slight modification, as standard terminology in the description of CD and these are given in table 1 in the previous section (page 4).

Research in the Indian population has also looked at the presentation of CD and one study (n=96) found that 67.7% of cases presented with diarrhoea, whereas 18.7% presented with refractory iron-deficiency anaemia and 9.4% with abdominal symptoms (Sood et al., 2003). The study clearly reports different modes of presentation from the European studies; however, the research itself has examined the hospital records of patients retrospectively and is therefore affected by the selection bias of a cohort of patients who were symptomatic enough to be hospitalised, thus excluding CD with minor symptoms.
A decade later, a study with prospective methodology and higher power (n=381) found that abdominal pain (and not diarrhoea) was a predominant presenting symptom (Bhattacharya et al., 2013). This study again selected patients from a tertiary centre and may have been affected by selection bias, because difficult and complicated cases are referred to tertiary centres. Similarly, a retrospective study (n=434) concluded that an atypical presentation was more common in Indian adult populations by comparing adults and children (Kochhar et al., 2012). Later, another study (n=233) retrospectively analysed health

records for the presentation of CD and found that 40% of adult Indian CD patients presented atypically (Sharma et al., 2013).

Earlier, a retrospective cohort study by (Butterworth et al., 2005) analysed 130 clinical attendances of CD patients and noted significant differences in the presentation between SA and Caucasian patients, including a younger age of presentation; this was later confirmed by another British study examining 2410 (SA n = 191) health records (Holmes & Muirhead, 2017). Butterworth et al., (2005) also reported a lower presence of IBS like illness, higher levels of alkaline phosphatase and lower DQ2-positivity status in the Asian (n=40) group, but the study was retrospective. It is likewise accepted that there is limited literature specifically looking into CD in the SA population (Yachha & Poddar, 2007, Malekzadeh et al., 2005) and further research is needed, with high-powered prospective studies and longer follow up.

Gastrointestinal features

There is huge variability in the gastrointestinal manifestations of CD between patients: it may present with diarrhoea, weight loss, abdominal pain, bloating and flatulence, yet it is accepted that none of these symptoms is specific for CD (van der Windt et al., 2010). Very rarely, a patient may present with severe weakness, abdominal pain, lassitude, electrolyte disturbance and dehydration as a result of severe diarrhoea; this is called a coeliac crisis (Parry & Acharya, 2010). There is evidence to suggest that CD presenting with abdominal symptoms is no longer the predominant clinical picture (Rampertab et al., 2006).

Abdominal symptoms such as discomfort, pain and accompanying bloating or increased flatulence are a common presentation of IBS (Wahnschaffe et al., 2001); hence, such patients may have been treated for IBS for years. This was investigated in a UK-based study (n=300) where patients with symptoms of IBS along with a similar number of asymptomatic healthy (age and sex matched) controls were tested for CD; 4.6% (n=14) were found to be suffering from CD in the IBS arm of the study compared with asymptomatic healthy individuals (Sanders et al., 2001). A later meta-analysis by Sainsbury and colleagues (2013) concluded that 38% of patients with CD had symptoms of IBS. The clinical point here is the need for a high index of suspicion for CD in patients presenting with IBS-like symptoms.

Extra-intestinal features

CD has a spectrum of presentation as explained above, and may also present with symptoms and signs that are extra-intestinal (EI) in nature (Gasbarrini et al., 2014), affecting different systems namely: skin (Collin et al., 2017), bone (Bianchi & Bardella, 2008), liver (Duggan & Duggan, 2005), thyroid (Metso et al., 2012), pancreas (Leeds et al., 2007), nervous system (Cicarelli et al., 2003) and heart (Emilsson et al., 2013). Moreover, EI symptoms are more common in elderly patients, being caused by chronic nutrient malabsorption; they can potentially affect any organ system. The figure below shows the involvement of different systems and related pathologies in relation to CD (Fig No 5).

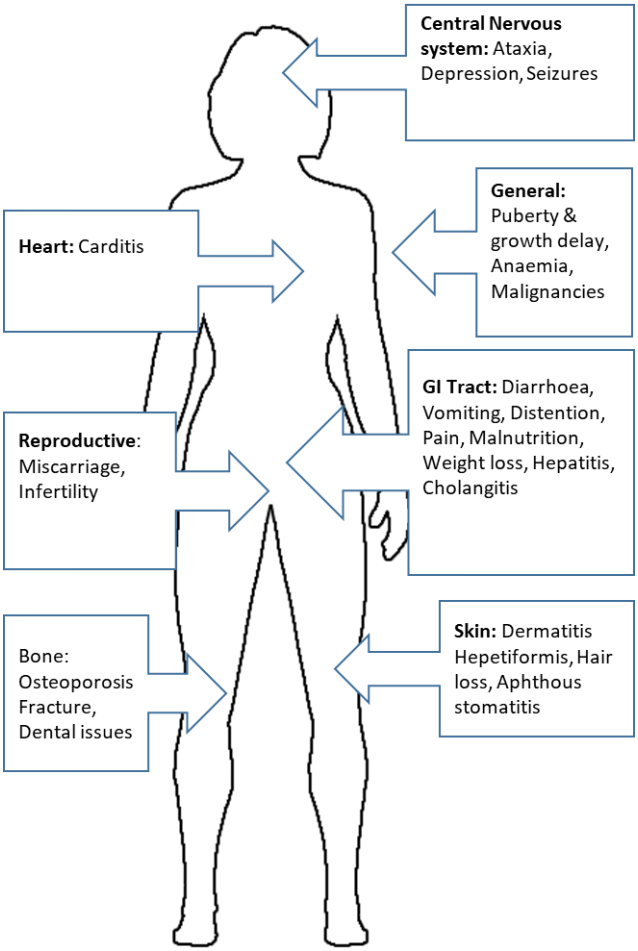

Figure 5: CD as a multi-system disease. Modified and redrawn from (Jnawali et al., 2016).

In terms of frequency, the most common EI presentations (>10%) are iron deficiency anaemia and skin diseases such as alopecia and Dermatitis Herpetiformis (DH). These are followed by (between 1 to

10%) osteoporosis, oral aphthous ulcers, dental issues, amenorrhoea and finally (<1%) rare issues such as: atopy, erythema nodosum, myositis and electrocardiogram abnormalities (Gasbarrini et al., 2014).

Anaemia is a common EI manifestation in all age groups (Smukalla et al., 2014) and may even be the presenting feature (Green, 2005). It is mainly caused by impaired absorption of iron leading to classical microcytic anaemia, but may well be multifactorial (Berry et al., 2018); occult gastrointestinal bleeding and anaemia of chronic disease may also play some role (Mant et al., 2006, Bergamaschi et al., 2008). It affects 10 to 41% of patients with CD (Harper et al., 2007, Dahele & Ghosh, 2001, Rampertab et al., 2006). The reported variability in these studies is related to the methodology used, definition of anaemia and multifactorial nature of anaemia. Anaemia associated with B12 deficiency (Harper et al., 2007) and folic acid deficiency (Howard et al., 2002) is rare.

Alongside malabsorption of iron, CD may also precipitate calcium malabsorption, leading to its effect on bone health (Capriles et al., 2009, Bianchi & Bardella, 2008), which may take several forms such as osteopenia (Di Stefano et al., 2000), osteoporosis (Mahadev et al., 2018, Laszkowska et al., 2018) and fracture (Olmos et al., 2008). Several studies have examined bone health in relation to CD and one concluded that there is a significantly reduced bone density between patients with CD and the normal population (Kavak et al., 2003). However, the study examined a paediatric group in which their bones are still in the growth phase, hence difficult to standardise; additionally it was a low powered study (n=34). In contrast to this, two earlier well-designed studies in this area estimated that 70% of patients with active CD have osteopenia (Corazza et al., 1995) and 25% have osteoporosis (Kemppainen et al., 1999b). The former study compared healthy volunteers (n=24) along with 31 patients with CD and concluded that the bone mineral density of untreated CD patients was significantly lower than that in the healthy volunteers. The latter study followed up a cohort of patients (n=28) for five years and noticed improvements in the osteoporosis with a GFD. A recent systematic review with meta-analysis concluded that there was no significant difference between osteoporosis in CD and the rest of the general population and questioned the rationale of routine screening, but accepted that this area needed more research (Mahadev et al., 2018).

A small but significant increase in fracture risk has been reported by a detailed systematic review and meta-analysis, but the author accepted the variability (both qualitative and quantitative) among the eight selected studies (n=20955) and urged the need for more research (Olmos et al., 2008). A subsequent prospective cohort study agreed with the findings of the meta-analysis (Heikkilä, et al., 2015). A recently

published study confirmed the increased risk of fracture in CD in combination with diabetes (Thong et al., 2018). Although the study had reasonable power (n=346), it was a retrospective cross sectional study. Similarly, another recent retrospective cohort study examining the risk of fractures in CD (n=1233) in comparison to healthy individuals (n=6167) did not find a significant difference (Canova et al., 2018), but the study only examined the heath records of adolescent patients. Based on this evidence, the BSG recommendation is to measure the bone density of patients with CD at regular intervals (Ludvigsson et al., 2014b).

In relation to the nervous system, both central and peripheral environments are affected by CD (Chin et al., 2003). One study found that neurological symptoms are 54% more common when compared to the general population (Zelnik et al., 2004); however, the study was questionnaire-based and may have been affected by recall bias. Sensory ganglionopathy (Hadjivassiliou et al., 2010) and ataxia, related to cerebellar dysfunction in CD (Bushara et al., 2001), are believed to be caused by immunological mechanisms (Green et al., 2005, Alaedini et al., 2002, Briani et al., 2008). Epilepsy and other seizure disorders are also common in CD (Pratesi et al., 2003). Likewise, CD can affect the reproductive system and may lead to amenorrhea, delayed menarche and infertility; these symptoms need investigation in CD patients as concluded by a meta-analysis (Tersigni et al., 2014).

Associated conditions

CD is related to a range of other autoimmune diseases such as Type 1 Diabetes Mellitus (T1DM) (Camarca et al., 2012), Down syndrome (Du et al., 2017), pulmonary haemosiderosis (Khemiri et al., 2008), recurrent pancreatitis (Ludvigsson et al., 2007) and thyroid disorders (Teixeira et al., 2014). Out of all the conditions, T1DM has the strongest association and the co-existence of CD and T1DM is partly due to the DQ alleles they share (Smyth et al., 2008). The prevalence of CD in T1DM patients ranges from 3-8% according to an early study (Cronin et al., 1997). A UK based study (n=113) found the prevalence to be 4.4%, which falls between the previously reported range of 3-8% (Goh & Banerjee, 2007). An Indian study (n=189) reported the prevalence to be 11.1%, which is higher than the reported range (Bhadada et al., 2011). Although there is a difference in power between these studies, the methodology is similar and it may be argued that racial differences exist, but more research is needed to arrive at a definitive conclusion.

CD is also associated with autoimmune thyroiditis and frequently leads to underactivity of the gland (Volta et al., 2001). IgA deficiency is also common (2%) and can lead to diagnostic confusion if only IgA tTG is measured, which thus leads to false negative results (McGowan et al., 2008). Similarly, inflammatory bowel disease (Yang et al., 2005) or microscopic colitis (Stewart et al., 2011) and CD may coexist and create diagnostic confusion.

CD affects the skin as well and there is a well-known association between Dermatitis Herpetiformis (DH) and CD. A papulo-vesicular and intensely pruritic rash, it involves the extensor surfaces of the skin and appears in early or mid-adult life, with a slight male preponderance (3:2); it is not commonly seen in children (Lionel, 2002). Furthermore, CD and DH are conditions that share pathogenesis and clinical features. They may well be parts of the same disease spectrum, as up to 10% of patients with CD have latent DH (Feldman et al., 2015). Skin lesions respond to Dapsone and a prolonged GFD may help to reduce the relapse rate of DH (Mansikka et al., 2018). Additionally, DH has an increased association with certain GI malignancies (Askling et al., 2002).

Diagnosis and management of Coeliac Disease

The symptoms and signs of CD are not always present, and when present are non-specific, as other malabsorption disorders share similar symptom combinations; this may lead to a diagnostic delay of up to 3 years (Paez et al., 2017). In all instances, when clinical suspicion arises, BSG suggests that serological tests are employed first (Ludvigsson et al., 2014b), namely IgA assays of anti-endomysial antibody (EMA) and tTG antibodies that target transglutaminase in tissue. These tests are cost-effective, widely available and have high sensitivity and specificity (Rostom et al., 2004). Many laboratories will measure total IgA, to avoid error in interpreting serological tests that may produce false negatives in IgA deficiency, in which case IgG-based tests may be offered (Korponay-Szabo et al., 2003) .

Upper Gastro Intestinal Endoscopy (UGIE) is the standard test to collect tissue samples for histopathological analysis, where duodenal scalloping may be noted as a gross mucosal feature of CD (Brocchi et al., 2002). Although small bowel biopsy is not a gold standard and may not be needed in the diagnosis of all cases of CD (Gülseren et al., 2018) because of complexity of levels of diagnosis in CD (Catassi & Fasano, 2010), it does add significant weight to the diagnosis (Caruso et al., 2014, McCarty et al., 2018) and is recommended by the BSG (Ludvigsson et al., 2014b). The BSG further states that small bowel biopsies are only useful if interpreted carefully within the clinical context, as VA is also seen in other pathologies (Ludvigsson et al., 2014b); isolated VA without any supportive serology, or even clinical symptoms, is a difficult clinical entity (DeGaetani et al., 2013) and HLA tests are indicated.

Although serological tests serve as diagnostic and prognostic tools, their diagnostic utility is interpreted in light of the clinical index of suspicion: in a patient with a low index the negative predictive value increases and vice versa. Because of the strong relationship between CD and HLA DQ2 or DQ8, genetic tests are undertaken when a patient has negative serology but has VA (DeGaetani et al., 2013) and a negative test excludes CD with great certainty in all age groups (Hadithi et al., 2007).

Micronutrients and malabsorption in CD

Severe malnutrition is rarely seen in current medical practice, but malabsorption of various micronutrients such as iron, calcium and vitamins is common in patients with CD (Haines et al., 2008, N. Kumar et al., 2004, Wierdsma et al., 2013). The reasons for malabsorption are complex: reduced surface area coupled with reduced secretion of intestinal cholecystokinin (Nousia-Arvanitakis et al., 1999) leads to impaired secretion of pancreatic enzymes, resulting in reduced absorption of fat-soluble

vitamins. The most clinically significant deficiencies are those of calcium and vitamin D (Bischoff-Ferrari et al., 2006), which lead to metabolic bone diseases ranging from osteopenia to osteoporosis (Di Stefano et al., 2000, Mahadev et al., 2018) and fracture (Olmos et al., 2008). In reported literature, 64% of men and 71% of women with CD exhibited vitamin D deficiency according to a study investigating bone mineral density (Kemppainen et al., 1999a) and hypocalcaemia was reported in 40% of patients in another study (Zanchi et al., 2008). Additionally, iron deficiency leading to anaemia is seen in 3% to 12% of patients with CD (Grisolano et al., 2004). Similarly, magnesium deficiency was noted in 19% of treated and 21 % of untreated CD patients (Rujner et al., 2004). Deficiencies of various other vitamins including B12, folate and vitamin K are occasionally observed (Kinsey et al., 2007, Qiu et al., 2006). Also recognised in association with CD are deficiencies of zinc, selenium, copper, vitamin E and vitamin B6, but these are rarely encountered in day to day practice (Haines et al., 2008, N. Kumar et al., 2004, Wierdsma et al., 2013, Högberg et al., 2009).

Management of CD

The only recognised treatment for CD is avoidance of dietary gluten (Rubio-Tapia et al., 2010). The term 'gluten free' (GF) means absolute elimination of all sources of gluten, which is found in wheat and related products (Rubio-Tapia et al., 2013), although it is accepted that food items containing gluten up to 20 ppm or less are considered as gluten free for standardisation purposes (Food and Drug Administration, HHS, 2013). Strict adherence to a GFD is the cornerstone of CD treatment (Rubio-Tapia et al., 2013) and this should be prescribed for all subgroups of CD, including symptom-free latent CD (Kurppa et al., 2014).

Food labelling and hidden gluten

Apart from products derived from wheat, barley and rye such as: bread, pasta, biscuits, cakes and pastries, gluten is also found in many other products including soups, takeaway meals, repackaged ready-to-eat meals and sausages (Denery-Papini et al., 1999), and even lipsticks and toiletries (Verma et al., 2018). The Food Standards Agency (FSA), in their most recent guidelines, define 'gluten free' food as one that has a gluten concentration of up to 20 parts per million (ppm) (FSA, 2012). More recently, in the United States, the Food and Drug Agency (FDA) has given a similar ruling on Gluten Free Foods (GFF) (FDA, 2013) and foodstuffs that remain below 100 ppm can now be labelled as low in gluten. In India, there is a statutory body of food regulation called the "Food Safety and Standards

Authority of India" and it requires a gluten level of less than 20 ppm for an item to be labelled GF (Dudeja et al., 2016). This threshold stands at 80 ppm in Australia, although an Australian study analysing the gluten contents of 127 commercial products found that up to 9% of food items in Melbourne may still contain high levels of gluten, despite being labelled GF (Halmos et al., 2018). A US based study also reported that 41% of samples were contaminated with gluten, despite being labelled GF (Thompson et al., 2010). Another study examined 74 samples from different sources and analysed them by using a gliadin competitive enzyme-linked immunosorbent assay and found that up to 60% of supposedly GF products were contaminated with gluten (Lee et al., 2014). Regardless of the cause(s) of contamination, this is a serious issue, as trace gluten may potentially cause inflammation of the small bowel mucosa and delay clinical recovery (Hollon et al., 2013). A recent systematic review examining selected studies (n=23) questioned the reliability of food items labelled as GF and suggested further research in this area (Falcomer et al., 2018).

A complete list of all GFF is difficult to present here, as it is being updated endlessly; nonetheless, the Coeliac Society UK publishes a directory of drinks, foods and other consumed products for members that contain gluten, along with a list of GF foods (Coeliac UK, 2018). The literature is renewed every month and sister organisations in other countries also have similar arrangements for their members (ACS, 2016, CA, 2015). Furthermore, patient-friendly mobile phone apps are available to guide patients in relation to a GFD (CSUK, 2016). The table below shows the list of typical GFF (Table No 3).

Table 3: A list of typical Gluten Free Foods (www.fitneass.com).

<table>
<tr><th>Produce</th><th>Meat (organic hormone free)</th><th>Nuts and Seeds</th><th>Baking/ Flour</th></tr>
<tr><td rowspan="4">Apple, avocado, baby tomatoes, banana, bell peppers, blueberries, broccoli, brussel sprouts, beets, carrots, cauliflower, celery, cucumber, ginger root, green onion, kale, lemon, mushrooms, pomegranate, red and yellow onion, turmeric root, small sweet peppers, spinach, strawberries and sweet potatoes.</td><td>Egg, chicken breast, ground turkey meat, shellfish, fish and bacon.</td><td>Almond, cashew nuts, walnuts, chia and sunflower seeds.</td><td>Coconut, arrow root, brown rice, almond, stevia, corn starch, baking soda, cream of tartar and tapioca starch.</td></tr>
<tr><td>Oils</td><td>Dairy</td><td rowspan="2"></td></tr>
<tr><td rowspan="2">Extra virgin olive oil, coconut oil, palm oil and avocado oil.</td><td rowspan="2">Almond milk, dairy produce and coconut milk.</td></tr>
<tr><td>Misc.</td></tr>
<tr><td></td><td></td><td>Dill, garlic, dates, lentils, nut butters, parsley, thyme, black beans and basil.</td></tr>
</table>

Aims of Treatment

The aims of treatment, as per The National Institute for Health and Care Excellence (NICE), include: relieving symptoms, replenishing micronutrients and reducing long-term complications (Downey et al., 2015). In addition to the established dietary recommendations for the treatment of CD, research is ongoing to genetically modify grain into a nontoxic grain (Bakshi et al., 2012). Furthermore, IL-15 blockers are also being investigated to determine whether it is possible to reduce the inflammatory cascade to reduce the mucosal inflammation (Maiuri et al., 2003). It is accepted that glucocorticoids have no role in the management of CD (Lara et al., 2003), although there is some room for their use in relation to refractory and acute life-threatening coeliac crisis (Dennis & Case, 2004). The salient features of management of CD are best presented as the mnemonic COELIAC, as explained in the table below (Table No 4).

Table 4: Basic steps in the management of CD. Modified from NIH Consensus Development Conference (June 28-30, 2004, Bethesda, Maryland, USA) on Coeliac Disease (James, 2005)**.**

1	**Co**nsultation with a skilled dietitian
2	**E**ducation about the disease
3	**L**ifelong adherence to a gluten-free diet
4	**I**dentification and treatment of nutritional deficiencies
5	**A**ccess to an advocacy group
6	**C**ontinuous long-term follow-up by a multidisciplinary team

Patient education is pivotal in the management of CD and repeated reinforcement is required by both a well-informed physician and a qualified dietitian, working together as a multidisciplinary team (MDT). In addition to advice to consume a GFD and possible major complications, the MDT should be vigilant for micronutrient deficiencies as well, such as: vitamin D, B12, folic acid, iron, zinc, magnesium and calcium, as suggested by a systematic review examining 22 out of 281 studies (Vici et al., 2016). However the exact clinical significance of this finding is not clear, especially in light of the long term deleterious effects of a gluten containing diet.

Refractory CD and complications of CD

CD that does not respond to treatment after excluding all possible exposure to gluten for a period of between 6 to 12 months (1-2%) is termed refractory CD (Malamut et al., 2012). This category has been further divided into two types and may well serve as a precursor for ulcerative jejunoileitis (UJ) (Biagi et al., 2000) and/or EATL (Cellier et al., 2000a). It is thus inferred that CD, refractory CD, UJ and EATL are all within a spectrum of diverse but pathologically-related conditions, stemming from the same clones of T cells (Ashton-Key et al., 1997). A detailed discussion on the pathophysiology of this condition is beyond the scope of this work; nevertheless, other complications of CD have been referred to earlier and include anaemia, osteopenia and osteoporosis.

In the past, CD was reported to be very closely related to the development of malignancies (Holmes et al., 1989), but subsequent studies have produced conflicting results. This may be explained by: the evolving definition of CD over time, patient selection, methodology adopted, years of follow up and age of the cohort studies. For example, CD was found to be associated with increased mortality in one Swedish study (n=29000); however, the methodology was retrospective and included older patients, who are generally prone to increased mortality secondary to cardiovascular and malignant causes (Ludvigsson et al., 2009). Likewise, studies have identified an increased risk of cancers in patients with CD, such as small intestinal adenocarcinoma, oesophageal cancer, melanoma and non-Hodgkin's lymphoma (Green et al., 2003). However, the study was retrospective and low powered (n=41), although a UK-based study reported similar findings (West et al., 2004). A later prospective study by Holmes et al., (2004) with 24 years of follow up and high power (n=5684) refuted these findings and no clear association with cancers was noted with CD. Indeed, there are conflicting reports in this area and further research is needed to determine the precise answer. Table below summarises the salient features of CD (Table No 5).

Table 5: CD in a nutshell. Modified from Krupa-Kozak (2014).

Coeliac Disease in Summary	
Prevalence	General population 0.5%–1.26%; children 0.31%–0.9%
Female:male ratio	Between 2:1 and 3:1
Trigger	Gluten (gliadins and glutenins, hordeins, secalins)
Causation	Genetic predisposition (HLA/non-HLA genes); environmental factors (infant-feeding practice, infections, drugs, socioeconomic factors)
Diagnosis	Positive histological testing (hyperplastic villous atrophy); positive serological testing (EMA, TGA antibodies); clinical remission on a strict GFD
Clinical presentation	Silent–asymptomatic, positive EMA or TGA antibodies; minor–unrelated symptoms or isolated symptoms of autoimmune diseases; positive EMA or TGA antibodies; major–frank malabsorption symptoms
Complications	RCD types I and II EATL
Associated disease	Type 1 diabetes mellitus; autoimmune thyroiditis; autoimmune myocarditis; Sjögren's syndrome; autoimmune hepatitis; primary biliary cirrhosis; selective IgA deficiency; Addison's disease; Down syndrome; alopecia areata; sarcoidosis; neurologic abnormalities; asthma and atopy; IBD; systemic and cutaneous vasculitis; psoriasis; inflammatory arthritis; vitiligo
Treatment	GFD; supplementation of identified deficiencies

Terms: EATL, enteropathy-associated T-cell lymphoma; EMA, endomysium; GFD, gluten-free diet; IBD, inflammatory bowel disease; IgA, immunoglobulin A; RCD, refractory coeliac disease; TGA, tissue transglutaminase

SECTION III

Dietary adherence in CD

The World Health Organization (WHO) defines adherence as *'the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider'* (Sabaté, 2003).

Attached to this concept is the word compliance, which is used in literature and to some extent interchangeably with adherence. Although both words are derived from Latin and entered the English language through old French, the word 'compliance' (Latin: *complier*) means to fill up (and hence to complete an action or process), whereas adherence (Latin: *adhaerere*) means to cling to, keep close or remain constant. Hence, when a patient is compliant with a GFD he follows it passively and does not necessarily own the process. On the other hand, when a patient is adherent, he actively gets involved or takes responsibility (Aronson, 2007) and the prescriber respects his right to choose (Cohen, 2009). In this text, the word "adherence" is given preference over "compliance" for this reason and this is also an established trend in the literature (Osterberg & Blaschke, 2005, Seng et al., 2015, Zschocke et al., 2014, Murage et al., 2018, Tovoli et al., 2018, Muhammad et al., 2019).

Non adherence with therapeutic dietary recommendations has been a major obstacle in achieving optimum control of disease activity in general. This applies particularly to non-GI areas such as cardiovascular, diabetes and metabolic medicine, where dietary adherence has emerged as a major factor affecting morbidity and mortality (Metz et al., 1997). An extensive meta-analysis of 569 studies (spanning over 50 years) investigating adherence to therapies, was conducted by DiMatteo (2004), who reported that the average non-adherence rate to medical therapies was 24.8%. Additionally, there are reported variations in adherence according to gender (Chung et al., 2006) and ethnicity (Natarajan et al., 2009). It is, however, accepted that studies done in this area are of variable durations, refer to different standards when measuring adherence and have diverse methodologies e.g. prospective, retrospective and interview based research (Desroches et al., 2010).

In CD, there are two aspects to the issue of adherence to a GFD: issues faced by the patients in adhering to this diet and also the difficulty for the treating dietitian in ascertaining whether a particular patient is adherent or not. In CD, strict adherence to a GFD is particularly important as there is no pharmacological treatment, in contrast to e.g. diabetes, where pharmacological agents (i.e. insulin and oral hypoglycaemics) are available. Additionally, it is an accepted notion that self-management by the

individual is of paramount importance. The role of the health team revolves around empowering individuals to self-manage the condition, as could be said for any chronic disease where active involvement by the patient is needed (Redman, 2005). In the case of CD, it remains relatively difficult to achieve success in these three areas: strict dietary adherence, patient autonomy and the ability of physicians to measure adherence objectively.

Advantages of adherence to a GFD

Symptomatic patients usually derive health benefits soon after starting a GFD (Murray et al., 2004) and this phenomenon was noted in an earlier research study, which demonstrated that, for the 70% of patients with classical symptoms, a GFD leads to symptomatic improvement (Pink & Creamer, 1967). More latterly, a research study (n=3031) also determined that the improvement is not limited to classical CD but also atypical-type disease (Kurppa et al., 2014). Furthermore, over the years research has shown that following a GFD: reverses the duodenal pathology, improves quality of life and reduces complications in patients with CD (Bernardo & Pena, 2012, Hall et al., 2013).

Histological recovery and a GFD

Histological improvement is the indirect reflection of reversal of malabsorption status related to CD. This is reflected in the clinical observation that iron deficiency anaemia improves following a GFD, suggesting increased iron absorption (Annibale et al., 2001). In addition, improvement in the duodenal histology is objective, as seen in one study (n=284) comparing Index and at least one subsequent biopsy of CD patients (Hutchinson et al., 2010), but the improvement is not necessarily complete, as suggested by another study (n=39) (Lee et al., 2003). This suggests that, for malabsorption to improve, complete histological recovery is not essential.

Annibale et al., (2001) in their prospective study (n=190) also noted that the recovery of villi was dependant on various factors such as: time between the biopsy and starting a GFD, severity of histopathological changes at diagnosis and age of the patients. A later study (n=65) with longer follow up reported this recovery to be 66% (Galli et al., 2014), which is two times higher than Lee et al. (2003) and this disparity may be explained by a difference in power, patient selection and the instruments used to measure adherence to a GFD. A recent study (n=65) by Belei and colleagues (2018), noticed that complete histological recovery (n=105) may take longer than a year after commencing a GFD. In

contrast, Lanzini et al., (Lanzini et al., 2009) in their prospective study (n=429), suggested that complete mucosal recovery was rarely (8%) possible. It is thus concluded that, although histological recovery takes a long time to progress (Hære et al., 2016), it improves beyond a critical point and malabsorption of nutrients is reversed.

Prevention of complications of CD and a GFD

CD has a set of complications related to malabsorption (such as anaemia), its effects on bone metabolism and yet another set of complications in relation to chronic inflammation in the SBM, driven by exposure to gluten; a brief overview will be given. Among the malabsorption group, calcium metabolism and related bone health is one important aspect that is affected in 50% of patients with CD (Zanchetta et al., 2016) and it ranges from osteopenia (Choudhary et al., 2017) to bone fractures (Heikkilä, Pearce et al., 2015, Olmos et al., 2008). Although earlier studies (Mora et al., 1999, Kemppainen et al., 1999b) denoted that initiation of a GFD improves bone health, a later study refuted these results (Pazianas et al., 2005), reporting significant issues with Bone Mineral Density (BMD) even after 4 years of a GFD. Additionally, another study reported that, although bone health is improved with a GFD, it is not restored fully as previously suggested (Szymczak et al., 2012).

This discrepancy may be explained by the selection bias (Pazianas and colleagues), where the population group (n=24) was entirely female and bone health is relatively poor as compared to males (Pietschmann et al., 2009). But despite that, recovery of bone health is dependent on histological recovery as reported by Larussa et al., (2017) and age of the patients, as patients diagnosed in later life have lower BMD (Paez et al., 2017). Although detailed discussion of bone health in CD is beyond the scope of this literature review, it is however accepted that a definitive answer regarding improved bone health has not been found, as two well-designed studies have indicated an improved outcome in relation to bone health for patients on a GFD (McGough & Cummings, 2005, Passananti et al., 2012), yet equally there is evidence that points at delayed bony improvement (Kaukinen et al., 2007, Larussa et al., 2017). It is, however, unclear whether this is clinically important, hence more research is needed in this area to look at the clinical outcomes such as bone fractures.

CD is found in up to 6% of patients with Iron deficiency Anaemia (IDA) (Karnam et al., 2004) and the reverse is also true, as IDA affects 10 to 41% of patients with CD (Harper et al., 2007, Dahele & Ghosh,

2001, Rampertab et al., 2006). A GFD leads to a 55.5% reversal of IDA, as suggested by a study (n=194) examining anaemic patients with CD who were started on a GFD, but it is time dependant and may take up to 12 months for complete recovery (Annibale et al., 2001). Fatigue, one of the principle symptoms of IDA, improves on initiation of a GFD in patients with CD, although this improvement is age selective, with more symptomatic improvement in the paediatric age group as compared with adults, as suggested by a study (n=737) examining a retrospective cohort (Jericho et al., 2017). Prospective studies are needed to determine the recovery pattern and time taken in recovery from IDA in CD.

CD is known to have other complications such as UJ (Biagi et al., 2000) and EATL, which develop in a subset of the CD population (Chander et al., 2018). Nevertheless, there is a paucity of research on the effect of a GFD on the reduction of these complications and this is partly due to their inherent rare nature and the requirement for longer follow up. Earlier research in this area was dogmatic about the protective nature of a GFD against cancers in DH (Lewis et al., 1996) as well as CD patients (Holmes et al., 1989); however, these were observational studies and not all the cancers referred to (Corrao et al., 2001, Green et al., 2003) had any significant association with CD.

EATL is a recognised complication of CD and Silano et al. (2008) followed up 1,757 CD patients (31,801 person-years) to examine the protective effect of a GFD. They reported that only nine patients developed EATL and concluded that a GFD is protective against EATL. The quality of evidence is weak: partly because of the power of the study, but also by reason of its observational nature. It is thus concluded that no strong evidence is available to determine whether a GFD is protective against any of the malignant or pre-malignant lesions of the small bowel in CD, and this is due to low incidence and variability in the quality of the studies (Ondrejka & Jagadeesh, 2016).

Based on the available evidence, a GFD may prevent these complications and patients should be advised about the protective effect of a GFD. Additionally, it is postulated that increased adherence with a GFD, by improving physical and psychological health for patients, may improve employability rates and also reduce health-related expenditure in the NHS, which was estimated by a cohort study (n=3646) to be 310.0 GBP per patient per year after the diagnosis of CD (Violato et al., 2012).

Health-related quality of life (HRQoL) and a GFD

HRQoL in CD depends upon the symptoms and the issues related to adherence to a GFD (Gray & Papanicolas, 2010). Adherence to a GFD may improve symptoms and may also improve HRQoL in patients (Kurppa et al., 2014), yet the tolerability of a GFD may also become an issue (Wolf et al., 2018). Combining these two concepts, it is inferred that a GFD has a variable effect on HRQoL in CD. Improvement of symptoms, for example in symptomatic patients after starting a GFD, also improved their HRQoL, as shown by a prospective study (n=132) using the 36 item short form survey (SF-36) and the Gastrointestinal Symptoms Rating Scale (GSRS) in newly diagnosed CD cases (Nachman et al., 2009). Additionally, a prospective multi-centre study using the Morisky scale and with relatively high power (n=366), subsequently confirmed these results (Casellas et al., 2015). It has likewise been shown that such an improvement in HRQoL is better in patients who are being followed up in a healthcare setting (Hughey et al., 2017). However, in contrast to this, a UK based case-control postal survey (n=573) indicated that 80% of adults with a mean duration of 8 years post-diagnosis did not report a significant difference in HRQoL and they found it difficult to follow a GFD (Barratt et al., 2011).

Burger et al., (2017) conducted a systematic review and meta-analysis (18 studies) and concluded that, although a GFD significantly improves HRQoL, it does not normalise it in CD. Studies included had used both generic and disease specific questionnaires, such as: the SF-356 Mental Component Score (MCS), the SF-36 Physical Component Score (PCS) and the psychological general well-being (PGWB) questionnaire; there was variability in the reported improvement depending upon which questionnaire was used. This was followed by a series of other studies which are enumerated in the table below (Table No 6).

Table 6: A brief outline of the studies investigating HRQoL in CD.

Main Author	N	Country	Description of Questionnaire	Characteristics of study/ comments
(Deepak et al., 2018)	60	India	(SF-12) and specific (CD-QOL) questionnaires	Reduced HR-QOL in adult CD patients, improves significantly on GFD
(Zysk et al., 2018)	251	Poland	Health-Related Quality of Life Questionnaire (HRQOL)	Females patients, economic scores inversely related low HRQoL
(Pratesi et al., 2018)	450	Brazil	Coeliac disease quality of life (CD-QoL)	Higher education related to better HRQoL
(Crocker et al., 2018b)	64	UK	Coeliac Disease Assessment Questionnaire (CDAQ)	Five stigmata of HRQoL defined: social, dietary, symptoms, social and worries
(Wolf et al., 2018)	80	USA	CD-specific measures assessment of HRQoL	Teenage, potential negative consequences of strict gluten-free diet
(Halmos, Deng et al., 2018)	5310	Australia	CDAT and quality of life data gathered	Dietary adherence was associated with better quality of life
(Oppenheimer et al., 2018)	273	Israel	Generic Disease Questionnaire (CODI) and the DISABKIDS Chronic Generic Measure (DCGM-37)	Paediatric study. Coping with low HRQoL in CD
(Mager et al., 2018)	243	Canada	HRQOL (Peds TM/KINDL and Celiac Disease DUX)	HRQOL in a multi-ethnic population with CD is comparable to healthy reference
(Lee & Clarke, 2017)	124	USA	CD-QOL questionnaire	No significant association between HR-QOL and laboratory parameters
(Skjerning et al., 2017)	422	Ireland	Coeliac Disease Quality of Life questionnaire (CDQL)	The CDQL comprehensively measures HRQoL
(Haas et al., 2017)	61	Canada	Patient-Reported Outcomes Measurement Information System (PROMIS) and global Short Form measure of QOL	HRQoL improved with text messages
(Borghini et al., 2016)	201	Belgium	Psychological General Well-Being Index (PGWBI) and Beck Depression Inventory (BDI) questionnaires	GFD induces an improvement of well-being (HRQoL)
(Rodríguez Almagro et al., 2017)	1097	Spain	Coeliac Disease Quality of Life questionnaire (CDQL)	There was a high level of congruence between quantitative scores and narratives

Journal articles published (in English) since 2016.

Several studies have included cross sectional analysis (Deepak et al., 2018, Zysk et al., 2018, C. Pratesi et al., 2018, Wolf et al., 2018, Halmos, Deng et al., 2018) or an intervention (Haas et al., 2017). Others have attempted to look at the role of different aspects of CD such as: better adherence to a GFD (Halmos, Deng et al., 2018, Haas et al., 2017, Deepak et al., 2018), education level (Pratesi et al., 2018), effect of a strict GFD (Wolf et al., 2018), economic aspects (Zysk et al., 2018), psychological wellbeing (Borghini et al., 2016) and HRQoL. Another has attempted to test the congruence between quantitative scores and narratives in mixed method research (Rodríguez et al., 2017). An earlier study reported that delay in diagnosis may also affect quality of life, which improves after a GFD (Norström et al., 2011). Also, if symptoms fail to improve, the quality of life remains low, as suggested by a German study examining 446 patients (Hauser et al., 2006).

The quality of these studies is nonetheless questionable, as the results may have been affected by the way HRQoL was measured, patient selection, power of the study and the duration of follow up. Yet, notwithstanding these factors, it is acknowledged that improvement in both psychological and physical symptoms improves HRQoL in a parallel fashion, but shows variable improvement, as suggested by the meta-analysis (Burger et al., 2017). The instruments used in these studies (such as: SF-36, EQ-5D and GSRS) were not disease specific and have their limitations when it comes to the specific aspects of CD.

A Norwegian study (n=422) found that there are differences in HRQoL in CD based on age and gender of the patients (Skjerning et al., 2017). The Oxford Working Group (Crocker et al., 2013) created a disease specific questionnaire, the Coeliac Disease Assessment Questionnaire (CDAQ), developed through in-depth qualitative interviews (Crocker et al., 2018b). The CDAQ is composed of five domains: social stigma, dietary burden, symptoms, social isolation and concerns related to CD. This reliable and valid coeliac-specific measure scrutinises all aspects of quality of life important to adults with CD (Crocker et al., 2018a). It is thus accepted that HRQoL is multifactorial and a detailed systematic review and meta-analysis of all available studies is needed.

HRQoL suffers decrements as well when a GFD is started and this is especially important in adolescent patients, who feel stigmatised and isolated when initiated on to a GFD (Olsson et al., 2008, Olsson et al., 2009). Similarly, in relation to comorbidities, initiating a GFD in patients with T1DM has a negative impact, as suggested by a study (n=73), although the questionnaire used in this study was nonspecific (Bakker et al., 2013). A Canadian study (n=3408) reported a further general negative impact of a GFD

on HRQoL, namely difficulty in obtaining a GFD, avoiding eating out and socialising, as well as event and travelling avoidance (Zarkadas et al., 2013). Additionally, a GFD is expensive to manage and that too can affect quality of life in economic terms (Zivin & Green, 2007a).

Evidently, total abstinence from gluten-containing products is not easy for patients to achieve and then maintain (Samasca et al., 2014). A GFD restricts several aspects of lifestyle and also has a negative effect on the way patients enjoy their food. Whitaker et al., (2009) in a UK based study (n=177) reported a variety of problems faced by CD patients using a questionnaire. Apart from the direct effect on the flavour of food, 54% referred to indirect effects and an additional economic decrement for buying GFF. In general, a GFD does take away certain freedoms in life in relation to eating and drinking, which does have indirect effects on factors such as where to eat and who to eat with. A Finnish study (Ukkola et al., 2012) identified the same trend as noted earlier by Whitaker et al., (2009), that asymptomatic patients had more negative views about the diagnosis of CD. What is more, there is gender variation in reported HRQoL and females tend to score lower on such questionnaires (Jacobsson et al., 2012). Interview-based research (n=16), which studied the effect of a GFD on women, similarly reported that affected female patients expressed a sense of loneliness and invisibility, especially when socialising with others (Roos et al., 2013). The reasons for such findings are not clear, however it should be noted that the studies have low power and may have suffered selection bias. It may therefore be concluded that studies to assess the negative effect on quality of life need more robust methodology: namely control groups, high power, validated instruments and qualitative methods to explore this area.

Cost attached to a GFD

By comparing the unit cost of gluten-free products (GFP) to gluten-containing products (GCP), the former were found to be relatively more expensive in a US based study (Stevens & Rashid, 2008a). This is despite the recent increased availability due to the demand for GF food items among consumers with Non-Celiac Gluten Sensitivity (NCGS) and as a fad diet (Reilly, 2016). A market based study by Mintel's Group (2015) has suggested that the GF industry has seen a growth of 136% from 2013 to 2015. The finding of increased cost of GFP was further analysed quantitatively and GFP were found to be 240% more expensive in one study and twice as expensive in another US based study (Zivin & Green, 2007a). In the UK the situation is similar and the prices are higher for GFP (Fry et al., 2018). In quantitative terms, a UK based study established this figure to be 76-518% (Singh & Whelan, 2011) and a recent

study has suggested this increase affects 91% of the GFF categories, which were 400% more expensive than their gluten containing counterparts (Jeanes & Hanci, 2018). The situation may well be similar in the rest of Europe, as suggested by a study from Greece, in which the cost difference was estimated to be 22–334% (Panagiotou & Kontogianni, 2017). This had a negative effect on HRQoL as suggested by a Canadian study (n=5912) exploring the day to day issues of patients with CD (Zarkadas et al., 2013).

The reported disparity may be explained by the methodological differences, but based on the above studies, a GFD is not an economically inexpensive option for patients. The practical point here is the effect of unaffordability of GFP on an economically deprived fraction of society and its effect on adherence to a GFD, especially when GFP are not available on prescription, or at best in insufficient quantities. A recent systematic review examining the economic burden of CD (49 studies) reported that initiation of a GFD leads to reduced visits to the GP and fewer missed working days (Mearns et al., 2018). More quantitative research is needed to explore this area by involving both patient groups and health commissioners.

Instruments used to measure adherence to a gluten free diet

Several instruments have been used in research studies and clinical practice to measure adherence to a GFD. The table below enumerates the methods used and detailed discussion of the evidence will be presented thereafter (Table No 7).

Table 7: Different methods used to measure adherence to a GFD.

Method		Description
Clinical		
	Symptomatic enquiry	Persistence of symptoms may indicate non-adherence (Sainsbury et al., 2013) but there exist asymptomatic patents as well (Kurppa et al., 2014, Sharkey et al., 2013).
	Serology	Persistently elevated anti-tTG denotes non-adherence with a GFD (Dipper et al., 2009) and the reverse is true (Leffler et al., 2007), but the evidence is not conclusive (Vahedi et al., 2003).
	Dietitian's assessment	Currently considered as gold standard (Pietzak, 2005) but subjective and patient dependant elements exist.
	Duodenal histology	Contrasting results suggested by (Biagi et al., 2014) and considered unnecessary by Pekki et al., (2017).
	Self-reporting	Clinician or dietitian enquiry
Research		
	Questionnaire	Abundant methods with variable results (Hall and colleagues, 2009), but comparable results to serology according to others (Leffler, 2009).
	Interview	Used in conjunction with questionnaire: variable results.
	Faecal/ urine test	Gluten immunogenic peptides in experimental stage (Comino et al., 2012, Moreno et al., 2017).

Clinical interviews and symptomatic enquiry

Clinical follow up is routinely used for assessment of symptoms and may be coupled with examination of indirect haematological markers in selected cases, such as: blood count, folate, B12, iron studies and liver biochemistry (Rubio-Tapia et al., 2013). Assessment of symptoms may be used in research, as suggested by a meta-analysis analysing seven studies (n=3383) where persistence of symptoms (especially abdominal) indicated decreased adherence with a GFD (Sainsbury et al., 2013). This strategy as a research instrument, however, has its own issues, as not all patients with CD have symptoms (Kurppa et al., 2014, Sharkey et al., 2013). Secondly, and more importantly according to Brar

and colleagues (2007), there is no correlation between mode of presentation of CD and degree of VA, as suggested by a study (n=499) examining duodenal histology.

Accordingly, there is a subset of the population with no symptoms at all, but with significant VA (Lähdeaho et al., 2011) and this may be explained by the patchy nature of CD and the requirement of loss of a critical absorptive area of the duodenum to cause symptoms. It is thus accepted that symptomatic improvement may not provide an accurate picture of adherence with a GFD in patients with CD. A Finnish study (n= 856) also described gastrointestinal symptoms persisting in a minority (6%) of patients despite strict adherence to a GFD for many years (Laurikka et al., 2016).

Duodenal histology

Traditionally, duodenal biopsies are obtained for the diagnosis of CD, although the clinical applicability of this practice has been questioned (Cammarota et al., 2006, Efthymakis et al., 2017). Biopsy assessment offers objective classification of the severity of CD based on research-established criteria (Ensari, 2016, Villanacci, 2015). A study (n=317) has highlighted the role of biopsy for follow-up, as (with an average 12 months follow-up) a proportion (8%) of patients who improved on serology, but not on histology, would have been deemed healed without duodenal histology (Biagi et al., 2014). In contrast, Pekki et al., (2017) in a nationwide follow-up study (n=760), did not find any significant advantage of performing repeat duodenal biopsies for GFD adherence in relation to: long-term adherence, symptoms, sero-positivity, questionnaire scores, frequency of fractures or malignancies. There is evidence to suggest that VA is not complete on follow-up biopsies as Lebwohl and colleagues (2014a), who identified 7,648 follow-up biopsies, reported that 31% of patients had persistent VA; but this was a retrospective study and it is not clear if the patients were adherent to a GFD or not. This area is controversial and contrasting studies with different methodologies exists for (Biagi et al., 2014, Elli et al., 2015) and against (Pekki et al., 2017) follow-up biopsies.

In addition, immunohistochemistry and flow cytometric analysis may be performed on the samples obtained for objectivity in diagnosis (Sanchez-Munoz et al., 2008, Patey-Mariaud De Serre et al., 2000). Despite the fact that duodenal biopsies are considered the gold standard research and clinical tool for adherence with a GFD, biopsies are invasive, expensive and time-consuming. Furthermore, this strategy may not be available everywhere and even with availability may not be suitable or even practical for every patient. It is therefore concluded that biopsy on its own is not a practical strategy for measuring

adherence in CD, but since differences of practice exist in this context, more research is needed in the form of a randomised study, which not only involves a pathologist but a trained dietitian who could assess adherence to a GFD.

Serological tests to measure adherence with a GFD

Several serological tests with high sensitivity and specificity are available for the diagnosis of CD in clinical practice and have been mentioned above. Their use for the purpose of measuring adherence with a GFD is also established in clinical practice (Rubio-Tapia et al., 2013). Among the serologies, anti-tTG has been used extensively in clinical practice for GFD-related adherence. It has been suggested that persistently elevated anti-tTG denotes non-adherence with a GFD, according to a study (n=182) with a 54 month follow-up period (Dipper et al., 2009). The reverse was indicated in another study (n=154), which reported that falling tTG was associated with adherence on questionnaire based assessment (Leffler et al., 2007).

Various studies have also examined the reliability of anti-tTG for this purpose: results show that there is a discrepancy between serological improvement and mucosal recovery. A study (n=95) examining the dietitian assessment and serology suggested that anti-tTG was not a reliable marker for occasional dietary transgressions (Vahedi et al., 2003). Moreover, a controlled cross-sectional study (n=87) examining this issue, reported persistence of VA despite the fact that serology was negative (Kaukinen et al., 2002b) and a later prospective study also confirmed these findings (Hopper et al., 2008). More latterly, Sharkey et al., (2013) also reported that serology is not an optimum surrogate marker of mucosal recovery, as the sensitivity of anti-tTG was 43.6% in detecting persistent VA when comparing the levels of anti-tTG and histological presence of VA. Although it was a high-powered study (n=595), as compared with previous studies, their methodology was retrospective. It is thus concluded that it is not currently clear how reliable serology is in assessing adherence to a GFD and more research is needed by establishing baseline adherence by an expert dietitian and then following patients up with periodic serology and dietitian assessment.

Other serological markers, such as EMA, have used a serological diagnostic adjuvant to test anti-tTG; they are nearly 100% specific, but they are less sensitive and their only other use is in the diagnosis of latent CD (Kurppa et al., 2009). Similar to anti-tTG, EMA also has issues with reliability in relation to measuring adherence with a GFD (Dickey et al., 2000). Likewise, antibodies against deamidated gliadin peptides (anti-DGP) have also been used in measuring adherence with a GFD, and their persistence in

the serum indicates non-adherence (Spatola et al., 2014). What is more, they are superior to anti-tTG for this purpose (Monzani et al., 2011, Volta et al., 2008). The American College of Gastroenterology has suggested that any of the above may be used as serological markers for assessing adherence to a GFD (Rubio-Tapia et al., 2013).

One particularly promising advance is the development of tests to measure GIP. These peptides are involved in the immunogenic reaction of CD and anti-α-gliadin G12 antibody (G12) may be detected in bodily fluids such as faeces and urine (Comino et al., 2012, Moreno et al., 2017); this has been used in monitoring adherence with a GFD in a research setting (Comino et al., 2016).

Novel Experimental Biomarkers of GFD adherence

Several other experimental markers are being developed, namely: citrulline (Blasco Alonso et al., 2011), intestinal fatty acid-binding proteins (Oldenburger et al., 2018), autoantibodies against pancreatic secretory-granule membrane glycoprotein 2 (GP2) (Laass et al., 2015), REG Iα (Planas et al., 2011) and plasma total alkylresorcinols (Lind et al., 2016). It is thus inferred that both EMA and anti-tTG are not reliable markers of histological recovery, but their base-line levels are important as they remain elevated with persistent transgression.

Use of questionnaires to measure adherence to a GFD

Questionnaire-based methodology has been used in CD to measure adherence with a GFD in multiple studies (Butterworth et al., 2004, Biagi et al., 2009, Leffler et al., 2009, Schilling et al., 2018, Ramirez-Cervantes et al., 2016, Espino et al., 2011) with slightly different methodological and questionnaire designs. Such a mode of delivery is considered economical when compared with other modes of delivery (Sinclair et al., 2012). (Edwards et al., 2009). A brief outline of the questionnaire-based studies is given in the table below (Table No 8).

Table 8: A brief outline of the studies investigating adherence to a GFD using a questionnaire (Q'r).

Main Author	n	Country	Description of Questionnaire	Characteristics of study/ comments
Rodrigues (2018)	35	Brazil	34 Item Q'r, assessing adherence and nutritional status	Paediatric/ adolescent cross sectional, 20% non-adherence
Schilling (2018)	64	Chile	Q'r by (Biagi et al., 2012) was used	Paediatric, cross sectional, 70% non-adherence, serology tested
Ramirez-Cervantes (2016)	56	Mexico	20 items with sub-items long Q'r. Adherence	Paediatric, cross sectional, 39% non-adherence, CD and non CD cohort
Fueyo-Diaz (2016)	306	Spain	CDAT (Leffler et al., 2009), 7 items, adherence	Adult, two-stage observational transversal study, 30% non-adherence
Rajpoot (2015)	146	India	Celiac symptom index (CSI), and SF-36. 36 points	Adult, Prospective randomised two groups, 35 to 47% non-adherence
Silvester (2016)	222	USA	20 Q's, complex, tables, adherence & knowledge	Adult, GFD Knowledge and effect on adherence, 21% non-adherence
Villafuerte.G (2015)	709	USA	CDAT (Leffler et al., 2009), 7 items	Adult, cross sectional, study knowledge and cost GFD, 25% non-adherence
Casellas (2015)	366	Spain	Modified Morisky et al., (1986) questionnaire	Adult, 23% non-adherence, Prospective, Quality of life and adherence
Bannister (2014)	150	USA	Biagi Questionnaire used	Paediatric, questionnaire, 12% non-adherence
Hall (2013)	287	UK	Mixed Q'r open and closed ended	Adult, Prospective, 40% non-adherence
Sainsbury (2013b)	189	Australia	CDAT (Leffler et al., 2009), 7 items, adherence	Adult, Prospective randomised intervention, 55% non-adherence
Charalampopoulos (2013)	90	Greece	3 section, Likert scale, simple Q'r	Paediatric/ adolescent cross sectional, 56% non-adherence
Biagi (2012)	141	Italy	Biagi Q'r developed. Five items, short	Adult, Biagi questionnaire was developed in this study, 20% non-adherence
Barratt (2011)	573	UK	Sf-36, Hospital anxiety scale and adherence	Adult, questionnaires used are generic, 34%% non-adherence
Espino (2011)	1,212	Chile	Interview and an online questionnaire, long	Adult, interviews and questionnaire, 8% non-adherence
Hopman (2009)	53	Netherlands	SF-36 and Food frequency Q'r. Adult	Adult, cross-sectional, questionnaires nonspecific, 34% non-adherence
Leffler (2009)	200	USA	CDAT was developed, 7 items Q'r. Adult	Adult, interviews and questionnaire, 8% non-adherence
Butterworth (2004)	130	UK	20 Items Q'r, non-adherence and causes. Adult	Adult, South Asians and White, 52 to 73% non-adherence

Journal articles published (in English) since 2014.

It is evident that several studies have examined adherence using a questionnaire and the number of participants in such studies range from under thirty by Högberg et al., (2003) to 1212 by Espino et al., (2011). Although several studies extracted data from questionnaires (Taghdir et al., 2016, Barratt et al., 2011, MacCulloch & Rashid, 2014, Dowd et al., 2014, Högberg et al., 2003, Garg & Gupta, 2014, Hall et al., 2013), there was no definitive description or template of the questionnaire available in the studies. Certain questionnaires were long (Butterworth et al., 2004, Rodrigues et al., 2018) and complex with sub-sections and appeared complex visually (Rodrigues et al., 2018, Silvester et al., 2016), whereas others were simple and short (Biagi et al., 2012, Leffler et al., 2009, Leffler et al., 2007). A few studies used questionnaires validated and developed by other investigators (Villafuerte-Galvez et al., 2015, Fueyo-Diaz et al., 2016, Schilling et al., 2018, Sainsbury, Mullan & Sharpe, 2013b).

The CDAT questionnaire by Leffler and colleagues (2009) is user-friendly, short (seven items), precise and designed to measure adherence with a GFD. It was developed by a panel in collaboration with different stake holders such as: gastroenterologists, dietitians, patients with CD and a psychologist, who assembled together to discuss factors related to CD with particular reference to their ability to affect adherence to a GFD. These factors were divided into five domains namely: symptoms, self-efficacy, motivation to observe a GFD, knowledge about GFD and perceived adherence to the GFD. A total of 85 statements were agreed upon, which were later reduced to seven statements. A lower score on CDAT denotes better adherence and the authors have suggested a CDAT score of 13 or more as the cut-off value for non-adherence to a GFD. The instrument was evaluated to have a 73.7% sensitivity, with a specificity of 76.7%. Its usefulness in a clinical setting has not been reported, despite the fact that it has the ability to evaluate non adherence and is better than anti t-TG in terms of sensitivity. A recent publication has also asserted that CDAT, in combination with the Biagi questionnaire, significantly outperformed IgA-TTG (p=0.01) in detecting VA (Lau et al., 2018). CDAT has been applied in several studies since its publication (Villafuerte-Galvez et al., 2015, Sainsbury, Mullan & Sharpe, 2013b, Fueyo-Diaz et al., 2016, Hære et al., 2016, Nazareth et al., 2015) and has proved to be a reliable instrument (Leffler et al., 2009, Fueyo-Diaz et al., 2016). It may be argued that CDAT as an instrument to measure adherence to a GFD is less biased, as the results are reliable and consistently similar in the above cited studies despite differences in the methodologies.

Biagi and colleagues (2012) also developed an easy and short questionnaire. Their study examined CD patients (n=141) on a GFD, and the sensitivity of the questionnaire for detecting non-adherence was

compared to serology and histology; lower scores were significantly associated with persistent VA. All patients in the study were well instructed about the GFD and the study endorsed the validity of the questionnaire in detecting non-adherence to a GFD. The questionnaire is simple to follow as it is depicted as a visual chart rather than questions. In comparison to CDAT, which has a holistic approach covering social and symptomatic aspects of CD, this questionnaire concentrates more on gluten ingestion. This questionnaire was subsequently used in two studies (Schilling et al., 2018, Bannister et al., 2014). The questionnaire, although simple, needs validation in high powered prospective studies.

Hopman at al., (2009) assessed adherence by using a food frequency questionnaire and this idea was subsequently transformed to develop a gluten-specific food frequency questionnaire (FQ-gluten4) by the same author (Hopman et al., 2012). Parents (n=74) filled 2 days' worth of food diaries for children aged between 1-2 years and these were compared with the FQ-gluten4. The mean amount of gluten intake based on the FQ-gluten4 was comparable to the food diary and it was concluded that the easy-to-use FQ-gluten4 may be a useful instrument in assessing gluten intake.

A Greek team of researchers designed a questionnaire of moderate length (15 items) to measure adherence rate (Charalampopoulos et al., 2013) and more recently an Iranian study team also measured adherence with a GFD by questionnaire, but the details available are limited (Taghdir et al., 2016). Among longer questionnaires, a Birmingham-based study evaluated adherence to a GFD in a 20-item questionnaire that holistically approached adherence employing clinical, social and economic terms (Butterworth et al., 2004). This instrument was used in the author's MSc Project (Muhammad et al., 2013) but it is, however, a long questionnaire as compared to the CDAT and Biagi questionnaires. Although research has indicated that detailed interview by an experienced dietitian coupled with serological tests is the optimal method to assess adherence to a GFD in day-to-day practice (Simpson & Thompson, 2012, Mehta et al., 2018), questionnaires such as the ones developed by Leffler and Biagi may have comparable sensitivity and specificity. This area, however, needs more research as the use of questionnaires may remove the need for repeat blood tests.

Adherence and non-adherence to a GFD

An assessment of GF dietary adherence by a dietitian is considered highly effective and is inclusive of assessing knowledge, behaviour while dining out and intent to adhere (Kurien et al., 2016, Mehta et al., 2018). Indeed it is considered a gold standard by some authors (Leffler et al., 2009, Sainsbury et al., 2015). Leffler et al., (2009) suggest that, although serological tests have very high sensitivities and specificities for the diagnosis of CD, they cannot replace dietitian evaluation in the assessment of GFD adherence.

Absolute non-adherence means ingestion of any amount of gluten (Muhammad, 2013). It is nonetheless acknowledged that patients with absolute adherence will ingest gluten, albeit inadvertently, and also some gluten (<20 ppm) is in GF labelled food (Bascunan et al., 2017). Hall et al., (2009) conducted a systematic review and noticed variability in the definition of adherence to a GFD, based on the methodology adopted by the authors. Some studies using interview or questionnaire techniques have defined adherence to a GFD as discretely variable and plotted on a scale (i.e. strict, partially or fairly strict and non-adherent) (Hall et al., 2009). These categories emerged from a prescriptive definition of an individual study based on the number of dietary transgressions over a defined time.

Variability has also been noted in reported adherence to a GFD. Hall and colleagues reported adherence ranging from 42% to 91% (Hall et al., 2009). The authors selected 38 adult studies by excluding papers involving combined data on children and adults, or if CD was not the primary illness under study. Since Hall and colleagues (2009), numerous studies have measured adherence applying different methodologies and found scores ranging from 53-76% (Leffler et al., 2009, Whitaker et al., 2009, Barratt et al., 2011, Holmes & Moor, 2012, Hall et al., 2013, Villafuerte-Galvez et al., 2015, Casellas et al., 2015, Rajpoot et al., 2015, Silvester et al., 2016, Sainsbury et al., 2018, Leffler et al., 2008).

Questionnaire-based studies that rely on self-reported adherence rates typically show higher adherence rates (Ciacci et al., 2003a), as do studies involving children (MacCulloch & Rashid, 2014). These studies have certain characteristics e.g. a clear majority of them had used CDAT (n=8) as their instrument to measure non-adherence to a GFD (Joelson et al., 2018b, Fueyo-Diaz et al., 2016, Sainsbury et al., 2018, Sainsbury, Mullan & Sharpe, 2013b). In this context, Villafuerte and colleagues (2015) determined that a CDAT score of 13 or above reflected non-adherence. Whilst the seminal study on CDAT (Leffler et al., 2009) suggested its validity for measuring non-adherence, Sainsbury and colleagues utilised

CDAT to assess the effectiveness of an intervention to increase adherence to a GFD (2016). The adherence measured by studies using CDAT ranges from 52% to 87% and there are differences such as power, recruitment, methodology and age of the patients, which may explain this wide variation. The table below shows an overview of these studies (Table No 9).

Table 9: Studies investigating adherence to a GFD using a variety of methods, after Hall et al., 2009.

Main Author	**n**	**Country**	Method	**Description, Adherence (Ad), factors affecting it.**
Leffler (2009)	200	USA	CDAT	Adult. CDAT was found to be valid.
Biagi (2009)	168	Italy	Biagi Q'r	Adult. Details limited.
Barratt (2011)	573	UK	Sf-36	Adult. Ad: 70%. GFD improves symptoms.
Holmes (2012)	1,305	UK	D'tn assessment	Adult. Ad: 88-92%. Audit.
Biagi (2012)	141	Italy	Biagi Q'r, serology	Adult. Ad: 74%. Discrepancy of histology & serology.
Charalampopoulos (2013)	90	Greece	Likert scale	Paeds. Ad: 44.4%, Child's age, parental knowledge.
Hall (2013)	287	UK	Q'r	Adult. Ad: 82%. Intentional > non-intentional.
Sainsbury (2013b)	189	Australia	CDAT	Adult. Ad: 62%. Intervention improves adherence.
Galli (2014)	65	Italy	Biopsy, serology	Adult. Ad: 81%. Histology take time to normalise.
Garg (2014)	134	India	Interview	Paeds. Ad: 65.5%. Age, mother's education, family.
MacCulloch (2014)	253	UK	Q'r	Paeds. Ad: Good.social events, camping out.
Rajpoot (2015)	146	India	CSI	Adult. Ad: 53.3%. FU increases it significantly.
Villafuerte.G (2015)	709	USA	CDAT, serology	Adult. Ad: 75.5%. CDAT score > non-adherent.
Webb (2015)	13,279	Sweden	Q'r, Serology	Paeds. Ad: 75%. All patients were 12 years old.
Casellas (2015)	366	Spain	Morisky	Adult. Ad 74.5%. Adherence improves symptoms.
Silvester (2016)	222	USA	Food Q'r	Adult. Ad: 82%. Lack of GFD knowledge.
Fueyo-Diaz (2016)	306	Spain	CDAT	Adult. Ad: 72%. CDAT highly valid for adherence.
Ramirez-Cervantes (2016)	56	Mexico	Q'r	Adult. Ad: 46%. Intentional consumption.
Taghdir (2016)	65	Iran	Q'r	Adults. Ad: 53.8%. Availability, cost, taste.
Sainsbury (2018)	7,393	Australia	CDAT	Adult. Ad: 60.5%.
Schilling (2018)	65	Spain	Biagi Q'r, serology	Paeds. Ad: 44% and 30%. Age, social events.
Halmos (2018)	7,393	Australia	CDAT	Adult. Ad: 61%. Age, male, knowledge, symptoms.
Joelson (2018b)	519	USA	CDAT	Adult. Ad: 87%. Mood may affect adherence.
Rodrigues (2018)	35	Brazil	Q'r and serology	Paeds: Ad: 80%. Social events.

Other than CDAT, studies have used the Biagi Questionnaire (Biagi et al., 2009, Schilling et al., 2018) for measuring adherence and reported a range of 30-74%. The low adherence reported may be explained by the adolescent age of the patients assessed by Schilling and colleagues (2018). The remaining studies have used their own questionnaires coupled with serology and interviews and have reported variable results.

Factors affecting the rate of adherence to a GFD

Research has indicated that causes of adherence and non-adherence to a GFD are numerous and multifactorial (Abu-Janb, 2018)and these include: socio-demographics, age at diagnosis, whether symptoms are present with gluten ingestion, practical difficulties associated with the GFD, and membership of advocacy groups (Hall et al., 2009, Leffler et al., 2008). Correspondingly, research has also indicated factors that may increase adherence to a GFD; a study conducted by Butterworth et al., (2004) who cited different reasons for poor adherence such as: understanding food labelling, affordability of GF products, obtaining GF products on prescription, obtaining sufficient GF products on prescription, and detailed explanation of CD in clinics. On the other hand, better adherence was identified as being related to membership of the Coeliac Society as well as regular dietetic follow-up. Later, Pietzak (2005) also reported factors affecting adherence and pointed to poor palatability of GF foods, confusing food-labelling practices, and common comorbidity and psychological burdens such as anxiety and depression in relation to poor adherence to a GFD. A systemic review by Hall and colleagues (2009) has ultimately identified and summarised many factors that affect adherence to a GFD including: socio-demographics, age at diagnosis and membership of advocacy groups. This area was further researched after the systematic review and several studies examined the factors responsible for poor adherence.

Among the socio-demographic factors, age is significantly associated with adherence to a GFD and shows variability in the adherence rate as suggested by the systematic review by Hall and colleagues (2009). In childhood, for example, adherence scores are better (Czaja-Bulsa & Bulsa, 2018, Jadrešin et al., 2008), as minors are fed by their parents; however adolescents do have issues with adherence as suggested by several studies (Levran et al., 2018, Schilling et al., 2018, Arnone & Fitzsimons, 2012, Olsson et al., 2008, Olsson et al., 2009, Errichiello et al., 2010). Schilling and colleagues (2018) examined 65 adolescent patients and assessed their adherence both serologically as well as through an adherence questionnaire; they found adherence to be low. The serology (tTG, EMA) suggested that the adherence was around 44% and the questionnaire reported it to be 33.1%. However a Swedish study (n=240) reported a high adherence rate (75%) among adolescents who were screen detected (Webb et al., 2015). An earlier review reported lower adherence but no figures were given (Arnone & Fitzsimons, 2012). Another study, using focus groups of parents and adolescent patients (n=45), reported that a GFD was a challenge for the adolescent and this was multifactorial (S. Meyer &

Rosenblum, 2018). This area needs more research as low adherence in this age group is multifactorial and detailed review of this age group is beyond the scope of this literature review. The table below shows the main factors affecting adherence to a GFD (Table No 10).

Table 10: Summary of factors affecting adherence to a GFD in patients with CD.

Factors	Description of main studies and finding
Social Peer pressure Social event, Camping out	Hall and colleagues (2009) suggested this to be a significant factor e.g. Social events and dining out. Following that, MacCulloch (2014), Rodrigues (2018) and Schilling (2018). Studies are questionnaire based ranging from 35 to 253 participants. Camping out and participation in social events have variable effects noted. Significant especially in the adolescent group. Adherence is better at home and school but worse when attending social events. Hall et al., (2009) also identified dining out as one of the factor affecting the adherence to a GFD.
Demographic Age, Gender, Ethnicity	Hall and colleagues (2009) suggested a role for advancing age to be associated with better adherence, but no significant relationship was noted for ethnicity or gender. Age at diagnosis also has significant positive correlation with adherence (Vilppula et al., 2011, Casella et al., 2012). Adolescents tend to have low adherence (Arnone & Fitzsimons, 2012). Males may be more compliant with a GFD (Halmos, Deng et al., 2018).
Psychological Depression Anxiety	Hall and colleagues (2009) reported increased levels of anxiety and depression in CD and no significant correlation with non-adherence. Later, (van Hees et al., 2013, Halmos, Deng et al., 2018) also reported increased prevalence of depression and a systematic review by (K. Sainsbury & Marques, 2017) suggested a negative effect of depression on adherence. Psychological traits may also affect adherence to a GFD.
GFD related Cost, Availability Label understanding, taste	Hall and colleagues (2009) did not establish a consistent relationship with cost and availability, but later studies were able to show that adherence is associated with high cost and low adherence. Availability was low in local Asian stores and it may affect adherence; understanding of food labelling is associated with adherence (Butterworth et al., 2004, J. Singh & Whelan, 2011, Zarkadas et al., 2006). Taste of GFF may affect adherence as suggested by Taghdir et al., (2016).
Family Mother's education Family support	Parental education about a GFD and CD plays a positive role (Charalampopoulos (2013). Similarly Garg (2014) and Khurana et al., (2015) reported the positive role of maternal education and the role of the nuclear family in increasing adherence in India.
Advocacy group & clinical follow up and symptoms	Hall and colleagues (2009) reported increased levels of adherence in members of such groups and later studies confirmed this (Leffler et al., 2008, Muhammad et al., 2017, Muhammad, 2013, Rajpoot et al., 2015). Clinical follow-up plays a significant role. Asymptomatic patients tend to transgress (Halmos, Deng et al., 2018).
Education	Positive correlation found with education (Leffler et al., 2008, Sainsbury et al.,, 2013b, Villafuerte-Galvez et al., 2015).

Patients diagnosed later in life had relatively good adherence (Vilppula et al., 2011, Casella et al., 2012). Vipul and colleagues (2011) reported conducting a study (n=54) of patients above 54 years of age and reported adherence of 85% 18 months after starting a GFD. Casella and colleagues (2012) examined clinical, serological and histological characteristics of patients above the age of 65 years (n=59) and reported even higher adherence (90%) in this age group. The consistency in these studies with longer

duration suggests higher adherence in this age group but, equally, there might well be other confounding variables which may not have been taken into account. Although it is accepted that extremes of age are associated with better adherence and adolescent age has relatively poor adherence, more prospective research is needed to tailor dietary advice for these age groups.

Research has indicated that the number of diagnosed females with CD is more than for males (Leffler et al., 2008), but there is no clear evidence to suggest that there are gender differences in relation to adherence to a GFD. Hall et al., (2009) in a systematic review, did not report any significant difference between genders in relation to adherence to a GFD. However, the studies selected (Dubé et al., 2005, Leffler et al., 2008, Ciacci et al., 1998a, Ciacci et al., 2002, Ciacci et al., 2003b) were not specifically designed to assess differences in the adherence between genders. In my MSc thesis (n=185) (Muhammad, 2013), no significant difference in adherence to a GFD was reported and a series of later studies also reported no difference in adherence between genders (Ramirez-Cervantes et al., 2016, MacCulloch & Rashid, 2014, Errichiello et al., 2010, Hall et al., 2013). It may be argued that there is a lack of consistent association between gender and adherence to a GFD.

Several studies have reported adherence in SA patients (Rajpoot et al., 2015, Chauhan et al., 2010, Yachha et al., 2006, Sachdev et al., 2002, Abbas et al., 2018, Khurana et al., 2015, Garg & Gupta, 2014, Masood & Shaikh, 2014b), but none has specifically compared the effect of ethnicity on adherence to a GFD. Additionally, it has been postulated that a separate set of dietary and cultural issues might affect adherence to a GFD among this ethnic group, such as: food habits, affordability and availability of GFF and composition of family structure (Rajpoot & Makharia, 2013, Garg & Gupta, 2014, Khurana et al., 2015). These inferences, however, are opinion based and more research is needed.

The first study to compare adherence between SA patients and White Caucasians reported that SA patients were comparatively less adherent to a GFD (Butterworth et al., 2004), but the study was relatively low powered (n=130). This study was replicated, using the same questionnaire, in my MSc thesis and no significant difference in adherence was reported (Muhammad et al., 2013). This is a contrasting result, despite the similar methodologies and cohort. It is clear that good quality and high-powered studies are needed to further explore adherence to a GFD in ethnic minorities resident in Britain.

A GFD does have associated financial costs (Singh & Whelan, 2011, Hanci & Jeanes, 2018) and details are explained in the relevant section above; but in relation to adherence this may have a negative effect, as suggested by studies (Pourhoseingholi et al., 2017, Villafuerte-Galvez et al., 2015, Estévez et al., 2016, Leffler et al., 2008, Zivin & Green, 2007b). Pourhoseingholi et al. (2017) conducted a questionnaire based study (n=213) and evaluated the detailed cost implications of CD on patients. Their cost analysis included visits to doctors, costs of tests (such as blood tests and endoscopy) and cost of GFF and suggested that the economic burden attached to CD may affect adherence to a GFD. Similarly, Lee et al., (2007) suggested that higher cost may be associated with reduced adherence to a GFD. Villafuerte-Galvez et al., (2015) surveyed 709 patients and 60% of the patients responded that cost may affect their adherence to a GFD to some degree. Estévez et al., (2016) examined the affordability of a GFD in the underprivileged quarters of Santiago, Chile and suggested that the higher costs of a GFD may well be an obstacle to achieving full adherence to a GFD. The studies above have suggested a relationship between higher cost and low adherence to a GFD, but there exist a lack of prospective studies to evaluate this area. One research suggestion would be to identify a group of non-adherent patients who had issues with affordability of GFF and then provide them with free GFF for a certain period, in order to assess the effect of correcting the cost factor. This is because adherence is a multifactorial issue (Hall et al., 2009, Leffler et al., 2008) and evaluation of a single factor (e.g. cost) and its effect on adherence needs a robust study design.

This suggestion was also included in an earlier UK-based study (Burden et al., 2015). At the time of writing, major changes are happening across all commissioning groups in the UK, with regards to the availability of GFP on prescription. Further research is needed to re-measure adherence within the population in general, especially among those who are from the lower socio-economic strata and those who were previously adherent.

Availability of GFF on prescription may also be associated with GFD adherence, as GFP is relatively expensive (Singh & Whelan, 2011). One study, using retrospective evaluation of GPs' electronic medical records, found that GFF are under-prescribed in the UK (Martin & Mercer, 2014). Moreover, provision of GFP on prescription might change, as suggested by a consultation exercise by the Nottinghamshire Health Authority (NSHA, 2016). Similar suggestions have also been put forward by the Oxfordshire Health Authority, in order to save £350,000 per year from local health budgets (OSHA, 2012). In August

2018, the Department of Health and Social Care (DHSC) initiated a consultation exercise on the prescription of GFP involving different stakeholders i.e. patients, charities, NHS organisations, members of the public and health professionals, to give guidance on reclassifying available GFP on NHS prescription (Department of Health and Social Care, 2018). This means that GFF (other than GF bread and GF mixes) may not continue to be prescribed in primary care in all areas of England. Concerns were expressed regarding the drop in adherence to a GFD as a result of these proposed changes, which came into force in December 2018. Stakeholders also pointed out that leaving this decision with the clinical commissioning groups (CCGs) may lead to variable practice and patients' access to GFF on prescription may well be a post code lottery. It is suggested that prospective studies are designed to see the effects of these changes on long term adherence to a GFD.

The pattern of clinical presentation (sub-clinical vs. clinical) has no significant effect on adherence (Viljamaa et al., 2005, S. D. Johnston et al., 2004). Screen detected (asymptomatic) patients have similar adherence to symptomatic patients, as suggested by a study involving 19 screen detected and 21 symptomatic patients (Mustalahti et al., 2002). A later study (n=97) with 14 years follow up also agreed and reported a rather higher adherence to a GFD among screen detected patients (Viljamaa et al., 2005). Yet another study (n=466) arrived at similar conclusions and reported similar adherence to a GFD in both groups (Paavola et al., 2012). A recent study reported that patients who are asymptomatic tend to transgress (Halmos et al., 2018). There is variability in the methodology of the studies cited and detailed review of this area is beyond the scope of this PhD, but needs more exploration with prospective questionnaire based studies which measures adherence objectively, for example via urinary GIP (Moreno et al., 2017).

Butterworth and colleagues (2004) in a questionnaire based study (n=130) reported a positive association of dietetic advice on adherence to a GFD. Hall and colleagues (2009) also arrived at the same conclusion in their systematic review. Barratt and colleagues (2011) in a case control study (n=573) implied that dietitian follow up is linked with better adherence to a GFD. Similarly, a study (n=617) from Quebec reported that only 44% of patients received dietitian advice and adherence to a GFD was positively associated with that advice (Lamontagne et al., 2001). Later, the role of follow up was also specifically evaluated in a prospective intervention study and it was found that repeated counselling at follow up has a positive impact on adherence to a GFD (Rajpoot et al., 2015). Despite

differences in the methodologies of the studies, it may be inferred that dietitians have an important role in adherence to a GFD, although prospective research with high power studies is required.

Other factors such as social interaction with others (dining out, frequenting meetings) may also have negative effects on adherence, as suggested by Black & Orfila (2011). The participants (n=146) in this study came from Coeliac UK and had 96% baseline adherence, but reported transgressions in situations where they had to interact socially. This phenomenon was previously noted by Hall and colleagues (2009) and has been confirmed in two similar studies (MacCulloch & Rashid, 2014, Schilling et al., 2018). Zarkadas and colleagues (2006) reported universal issues of adherence to a GFD while travelling and dining at friends' houses, where patients with CD were found to avoid travelling (38%) because of their illness. This is because a GFD imposes restriction on QoL (Rose & Howard, 2014) and it may not be possible to adhere to a GFD in all situations.

Hall and colleagues (2009) reported increased levels of adherence in members of coeliac advocacy groups such as Coeliac UK and later studies confirmed this (Leffler et al., 2008, Muhammad, 2013, Rajpoot et al., 2015). It is however not clear what causes this increased adherence i.e. do naturally adherent patients join the advocacy groups or is it the education and motivation from the advocacy groups which increases adherence? The first theory is difficult to test, but the latter may be verified by reviewing the literature of all the advocacy groups and looking for common themes and then comparing their adherence rates. Such themes may then be included in an educational intervention programme which may be given to non-adherent and control groups to ascertain its effectiveness.

Depression is common among patients with CD (van Hees et al., 2013) and may have a negative effect on adherence, as suggested by a systematic review (Sainsbury & Marques, 2017). However, the quality of the systematic review is questionable – as admitted by the authors – because the number of studies included was very limited and they had strict/limited inclusion criteria. Improvement in depression symptoms was not shown to be a significant factor in increasing or maintaining adherence with a GFD, as shown in earlier studies (Ciacci et al., 1998b, Fera et al., 2003), although a later study (Abenavoli et al., 2006) showed opposite results; but there is a paucity of research in this area and more studies are needed.

Among other factors, an important but potentially modifiable cause of low adherence is lack of awareness about gluten-containing foods (Silvester et al., 2016) and studies have reported the effect of

knowledge on adherence to a GFD (Leffler et al., 2008, Lamontagne et al., 2001, Casellas et al., 2006, Zabolotsky et al., 2017). Similarly, the taste of GFF may also decrease adherence to a GFD (Taghdir et al., 2016). It is however accepted that studies in this area are methodologically flawed, with low power and un-validated questionnaires. It is felt that this area needs interview based research to evaluate these causes further. Clinical follow-up plays a significant role.

In summary, causes of low adherence are diverse and affected by many factors, and may even be different for particular ethnic groups. The evidence for different causes, as suggested by studies, is limited by the methodologies utilised and because the studies have used different instruments. A comprehensive meta-analysis may be conducted to identify the factors from different studies and classify them into modifiable (e.g. knowledge, GFF availability and membership of advocacy groups) and non-modifiable factors (e.g. age, sex and ethnicity) and the intervention programmes that are designed to rectify the modifiable factors in order to improve the adherence to a GFD.

There is a very limited body of literature about the adherence to a GFD of SA with CD, and it is important to understand adherence among SA based on their specific ethnic characteristics. Several factors may differentiate a typical Indian patient from their European counterpart. A typical Indian family is a nuclear family (Garg & Gupta, 2014); fresh food is cooked and consumed on a daily basis (Counihan & Van Esterik, 2012) and eaten at home, whereas this may not be true for a typical European family, as suggested by a study examining the consumption of food outside the home in ten European countries (Orfanos et al., 2007). Eating at home among SA families is a known cultural trend (Aloia et al., 2013, Goyal & Singh, 2007), but this trend is changing towards a westernised diet, as suggested by research (Holmboe-Ottesen & Wandel, 2012, Wandel et al., 2008, Namvarasl & Chakravarty, 2018). Moreover, a typical Hindu family may be vegetarian (Namvarasl & Chakravarty, 2018) and consume cereals, pulses, spices and vegetables, whereas a Muslim family may consume meat, fish, poultry and vegetables depending upon availability and affordability (Bhatti et al., 2007). Wheat and rice are staples of the diets and, again depending on affordability, dairy products and seasonal fruits are also consumed.

In order to evaluate adherence rates and barriers to adherence in the Indian population, one well-designed Indian study (n=146) recruited both treatment-naïve participants (n=54) and those on a GFD (n=92) and found the main cause of non-adherence was reported to be non-availability of a GFD, although they did not specify which component of the diet was not available (Rajpoot et al., 2015).

However the results may well have been affected by selection bias, as patients were drawn from specialised CD clinics, which tend to be attended by motivated patients.

There exists a paucity of food labelling in India, with the exception of the main cities, and knowledge about a particular food item is often anecdotal (See & Murray, 2006, Saturni et al., 2010). Additionally, certain practices in grinding mills may encourage cross-contamination of GF products with gluten, and such flour could reach the UK and be sold in Asian shops. This area needs research by designing a study to measure the gluten content of rice flour available in the UK, for example, from randomly collected samples. It has also been observed that newlywed young women face adherence issues while living among her husband's family members, whose knowledge of CD is non-existent or negligible, and she may be required to prepare food for the whole family (Rajpoot & Makharia, 2013). This area again is based on anecdotal observations or opinions in reviews and needs further interview based research.

The first analysis of SA immigrants with CD was undertaken in a Birmingham-based study which specifically looked into the question of adherence with a GFD in SA (n=40) as opposed to Western Caucasians (n=90) (Butterworth et al., 2004). The SA were reported to be dissatisfied with the services offered and often missed follow-up appointments in comparison to Western Caucasian patients. Indeed, the questionnaire return rate was low, as observed previously (personal communication with Professor John F Mayberry) in relation to other studies involving SA.

SECTION IV

Interventions to improve adherence to a GFD

Following a GFD is not just a matter of changing the diet, but involves the patient changing their entire lifestyle; further research is needed for the development of an easy to understand, cost-effective and patient-friendly intervention to improve adherence to a GFD. To date, only nine intervention programmes have been reported with reference to GFD adherence in the literature and three particularly target improving adherence to a GFD. The studies have approached the issue (increasing adherence to a GFD) from different angles and the majority of them lack general applicability and are not clinically relevant for day to day practice. Computer based interventions, for example, are technology dependant and may only be able to target a proportion of patients affected by CD. Similarly, studies which have either included only White Caucasians or SA may not be fully interchangeable, as there are dietary and cultural differences in both communities; although the dietary ingredient in question (wheat) is the same, the products produced from it vary between different cultures. Likewise, studies which have either targeted patients with psychological issues and CD or diabetes with CD may also lack generalisation for the vast majority of patients whole present only with CD. Lastly, but importantly, there exists variability in health delivery models in different countries and this too may have an effect on the delivery of a particular intervention, when for example it is developed in one country but applied elsewhere.

It is however accepted that the issue (i.e. low adherence to a GFD) has been recognised and some efforts have been made in the form of interventions to increase adherence. These studies have been grouped according to the approach they have used to increase adherence to a GFD. A detailed critical review of each study will be given, followed by the conclusion drawn from it. Salient features of these studies have been compared in the table below (Table No 11).

Table 11: Interventions to improve adherence to a GFD in CD.

Study	N	Method of assessing adherence to a GFD	Key Findings	Strength/ weakness
Addolorato et al., 2004. Rome, Italy. To evaluate the use of psychological support counselling to improve affective disorders and gluten-free diet adherence in CD.	66	**Instruments:** State-Trait Anxiety Inventory test Y-1 and modified Zung Depression scale. **Intervention:** Psychological support 2-6 weeks; FU for 6 months. Non randomised and lack of ethnic population.	Significant improvement in adherence in intervention group as compared to non-intervention (39.4% vs. 9.1%; P=0.02).	Lack of general applicability. Depression was not defined in relation to lack of adherence and methodology to measure adherence was not objective. Mixed patients with anxiety and depression hence no clear distinction about the mechanism of improvement of adherence.
Meyer et al., 2004 Leipzig, Germany. Comparative analysis of conventional training and the computer-based interactive training program (CBITP).	64	**Instrument:** Knowledge questionnaire. Indirect inference of adherence. **Intervention** CBITP vs conventional training groups; FU 3 weeks.	Both intervention and control groups increased knowledge about CD. However, the intervention group performed significantly better.	Randomised study but adherence was not measured directly and clinical value is uncertain. Short follow up (3 weeks) and dependant on technology and computer literacy.
Ring Jacobsson et al., 2012, Linköping, Sweden. Effects of patient education on the psychological well-being of women with CD in remission.	106	**Instrument:** Psychological wellbeing test and validated questionnaire. **Intervention** Two groups randomised. 10 sessions. Wellbeing checked at 10 and 25 weeks. Omnigender (female).	Significant improvement in psychological well-being at 10weeks, whereas the controls given usual care reported a worsening in psychological well-being.	Randomised study but adherence was not measured. Clinical value of the study is questionable as psychological wellbeing was not correlated with adherence. Generalisation is questionable.
Sainsbury et al., 2013b and 2015 Sydney, Australia. To test the effectiveness of an interactive online intervention to improve GFD adherence in adults with CD.	189	**Instrument:** CDAT. **Intervention** Online intervention "Bread and Butter." Intervention group (n=101) and control (n=88). 3 month follow up.	Significantly improved GFD adherence, and GFD knowledge following the treatment period compared to control group (p=<0.001).	Randomised study, comprehensive and direct assessment. Selection bias as patients recruited from Coeliac Society and no ethnic population. Technology dependant and limited clinical value.
Assor et al., 2015 Ottawa, Canada. To evaluate the safety and efficacy of a GFD in patients with CD and to assess adherence and facilitate evaluation of a GFD.	NK*	**Instrument:** Dietary interview (visits), CDAT, Serology **Intervention** Dietary curriculum; 2, 3 and 4 months visits.	The study did not publish the results so it is not clear what the outcome of the intervention was.	Randomised study, comprehensive assessment, only asymptomatic CD, generalisation and clinical value questionable. Longer follow up but results never published.
Rajpoot et al., 2015. Delhi, India. To assess the level and barriers to adherence and role of clinical follow-up in adherence.	172	**Instrument:** Coeliac symptoms index and adherence questionnaire. **Intervention** Repeated counselling given; FU 6 months.	Significant improvement in adherence from 35% to 92% at 6 months.	Randomised, medium (6 months) FU. Has clinical value but only Asian patients. Lacks counselling details.
Pekki et al.,2017. Temper, Finland. To evaluate predictors and significance of long-term follow-up i.e. adherence.	677	**Instrument**: Serology and validated questionnaire. **Intervention:** Followed up groups observed**.**	No significant difference between the FU and NFU groups.	Non randomised and retrospective. Selection bias in survey recruitment. Longer follow up but generalisation questionable. May have clinical value if repeated with better methodology.
Haas et al., 2017 California, USA. To determine the impact of the Text Message on adherence.	64	**Instrument:** CDAT serology. **Intervention** Text Message Educational Automated Adherence Help. 3, 6 and 12 months FU.	There was no statistically significant difference in patient-reported or objectively measured GFD adherence.	Randomised, medium (6 months) FU. Has clinical value. Cost effective.
Wolf et al., 2019 New York, USA. To determine the impact of gluten sensing device (Nima) on adherence	30	**Instrument:** Gluten sensing device	Prevented users for consuming gluten in food items thought to be gluten free.	Randomised, three months FU but low powered. The testing was time consuming.

NK* Not known as the study is ongoing

Role of Follow-up in increasing adherence to a GFD

Two studies have assessed the role of follow-up (FU) by health professionals and its effect on adherence to a GFD and come up with contrasting results. A study from Finland (n=667) by Pekki and colleagues (2017) evaluated predictors and the significance of long-term FU in relation to adherence. They reported that there was no significant difference between the groups (regular FU 6.3% (n=94) vs. no FU 15.1% (n=527), respectively, $p = 0.343$; $n = 95$). Although not explained, patients without FU reported more symptoms (16% vs. 26%). There was no major difference between the ages, adherence to a GFD or sero-positivity of the groups. It is not clear if they took into consideration all reported confounding variable such as: membership of a coeliac advocacy group, accidental intake of gluten and level of knowledge about different GF and GCP.

Rajpoot and colleagues (2015) prospectively followed CD patients (n=146) who were both treatment naïve (n=54) and already on a GFD (n=92) for the preceding six months and reported that FU and counselling lead to a decrease in celiac symptom index (CSI) score, suggesting better adherence. Additionally, improvements in haemoglobin and albumen levels were also noted. Both groups in the study showed improvement from the baseline; the FU group showed a significant increase in adherence (from 53.3% to 92.4%) to a GFD in comparison to the treatment naïve group (64.8 % to 96.3%). Note that these findings are very different from the results reported by Pekki and colleagues (2017).

There are methodological differences between the two studies which may explain the conflicting results. The study by Pekki and colleagues (2017) was mainly a retrospective observational study and did not administer any intervention, but compared the adherence in FU and non-FU groups, whereas the study by Rajpoot and colleagues (2015) was prospective; it also compared availability and affordability of GFP in both groups, which was same. The role of FU in relation to better adherence has previously been reported (Wylie et al., 2005, Butterworth et al., 2004) and BSG (Ludvigsson et al., 2014b) as well as ACG (Rubio-Tapia et al., 2013) also assert this. The possible benefits of FU need more research by conducting prospective studies and comparing groups in terms of validated instruments for adherence to a GFD. Duodenal biopsies and serology may also be used to objectively evaluate the role of FU in achieving adherence to a GFD.

Role of gluten detecting device to increase adherence to a GFD

The principle of this study (Wolf et al., 2019) was based on assumption that increasing the knowledge motivated people about gluten in a food item, thought to be gluten free, will deter them from eating gluten hence, increasing their adherence to a GFD. The group recruited 30 participants and the device was charged with disposable capsule by the participants each time the food item was tested. This would help in identification of the gluten contents (set at > 20ppm) of the food item. The researcher found subjectively reported increase in adherence to a GFD by the participants. Although, attractive in theory, the device (Nima) was found to be time consuming and increased anxiety among the participants. Moreover, the study was low powered may have selection bias. Additionally, the device only targets motivated patients and helps to avoid only accidental intake of gluten. Furthermore, it is concurred that the device will have attached cost to it and its exact role in the long term control of adherence is not clear at this stage.

Role of computer based education in increasing adherence to a GFD

Two studies have assessed the role of computer based literacy programmes as an intervention to increase adherence to a GFD and reported similar results. Meyer and colleagues (2004) utilised a computer-based interactive training program (CBITP) combined with interactive exercises to see their effect on improvement in knowledge about CD and not adherence. Patients (n=64) were randomised into two groups and one received CBITP whereas the other only received written instruction. Although both groups were noted to have increased in knowledge, the CBITP group showed significantly better improvement in knowledge than the control group. Notwithstanding the fact that randomisation had been included in the study design, several issues were identified that diminished the applicability of this study. Most notably, increased knowledge was assumed to be a surrogate for increased adherence, although it is accepted (even by the author) that adherence to a GFD is a complex interplay of multiple factors (Hall et al., 2009); the clinical value of this study is therefore questionable. In addition, the way that the cumulative score was measured gives no clear information about individual key areas of CD knowledge. For example, a patient may score highly in multiple areas about the GFD, but may score poorly on their knowledge about a GFD in a restaurant, and thereby still ingest gluten. This study, like the previous one, is an indirect study and there is no evidence to show that the effect recorded had any long-term clinical implications.

These issues were addressed in a later study (Sainsbury & Mullan, 2013b): a well-structured, goal-directed and objective RCT to improve the adherence rate for GFD in CD patients (n=189) who were divided into intervention (n=101) and control (n=88) groups. Of the 101 intervention participants, 50 (49.5%) completed the intervention and the remainder were either lost to FU (n=31) or partly participated in the study (n=21). They devised a web-based intervention, called 'bread and butter' and the primary outcome was to improve GFD adherence. Three months' FU was arranged for the patients. CDAT was used to measure GFD adherence, which showed improvement in the intervention group (p<0.001) and remained unchanged in the control group (p=0.67). In addition, they noted an increase in knowledge about CD in the intervention group. The comparative adherence scores, both pre and post intervention, are shown in the Figure below (Fig No 6).

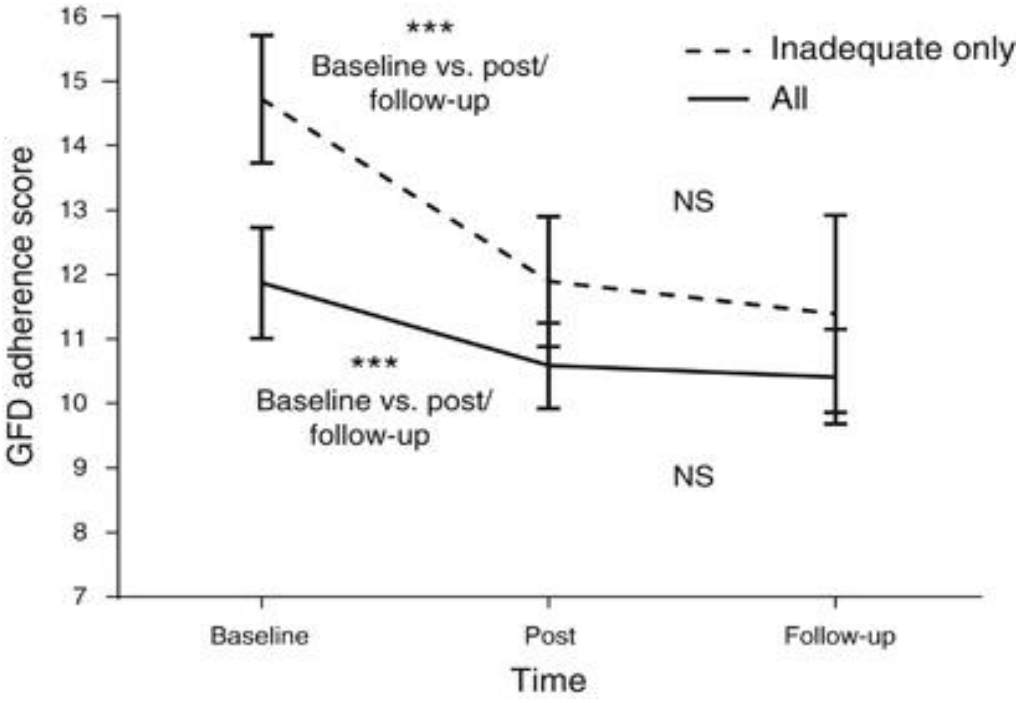

Figure 6: Baseline, post-intervention, and three-month follow-up adherence scores. Note: Fixed line (all) refers to analyses conducted on the sample of intervention group participants (n=101) who completed the intervention and responded to the 3-month FU survey (n = 46); baseline vs. follow-up: t 46 = 3.63, P < 0.001; post versus follow-up: t 46 = 0.53, P = 0.600. Dashed line (inadequate only) refers to analyses conducted on the subsample of intervention participants who had inadequate adherence at baseline and completed the intervention and 3-month follow-up survey (n = 18); baseline vs. follow-up: t 18 = 4.50, P < 0.001; post vs. follow-up: t 18 = 0.70, P = 0.497; GFD adherence scores range = 7 – 35; higher scores indicate poorer adherence; inadequate adherence defined as a score of 13 or higher; * * * P < 0.001. GFD, gluten-free diet. Sainsbury and colleagues (2013).

Sainsbury and colleagues (2013) selected patients from the Coeliac Disease Society (CDS) and social media which may thus introduce selection bias, as patients from such a society have better adherence to a GFD as suggested by research into this area (Leffler et al., 2008, Muhammad, 2013, Rajpoot et al., 2015, Hall et al., 2009). Furthermore, both studies employed web-based methodology and hence computer literacy might well be an issue in an elderly group that forms a significant proportion of the adult UK population with CD (West et al., 2014). Regardless of this, the latter study provides both a theoretical as well as a practical baseline for future design and execution of studies in this context. Using the same cohort, Sainsbury and colleagues (2015) also reported in a follow up publication, that baseline intention and GFD adherence were strongly associated with FU intention and adherence to a GFD.

Role of text messages in increasing adherence to a GFD

Following the same line, Haas and colleagues (Haas et al., 2017) evaluated the role of text messages in relation to increasing adherence to a GFD (n=64). The text message group received 45 unique text messages over a 3-month study period, while the control group received standard care. Adherence was measured with serum anti-tTG (IgA) and deamidated gliadin peptide (IgA) levels and no significant difference was noted between the groups. The study, however, could be criticised for the short duration of FU (3 months) and over-reliance on serology to confirm adherence. The role of serology to detect non-adherence has been questioned (Vahedi et al., 2003, Kaukinen et al., 2002b, Hopper et al., 2008, Sharkey et al., 2013). Additionally, patients' ages ranged from 12 to 24 years: a demographic which has low adherence generally (White et al., 2016, Schilling et al., 2018) and which may weaken the general applicability of this study.

Role of improving psychological wellbeing in increasing adherence to a GFD

Two further studies concentrated on improving the psychological condition of CD patients and measured the indirect outcome i.e. improved adherence to a GFD. In the first study (n=66), newly diagnosed CD patients with anxiety and depression were divided into two equal groups and followed up for 6 months (Addolorato et al., 2004). The intervention arm received psychological support, whereas the control group was only followed up in the clinic. At six months, the intervention group was reported to show better adherence with a GFD as compared to the non-intervention group (39.4% vs. 9.1%; P=0.02). However, there are many flaws to this study, which bring into doubt the general applicability of such psychological support. Adherence to a GFD, for example, was not measured objectively e.g. by a questionnaire or combination of serological and histological assessment. Additionally, a specific

subgroup of patients with CD was selected, which was not representative of the whole group in terms of behaviour, attitude or even knowledge about adherence to a GFD. Furthermore, the mechanism through which improvement in depression is related to an increase in adherence was not explored. This raises questions about the clinical value of this study.

The second study (n=106), a randomised controlled trial, recruited only women with CD, all ≥ 20 years old and on a GFD for more than 5 years (Ring Jacobsson et al., 2012). The aim of the study was to assess the effects of an active method of patient education on the psychological well-being of women with CD in remission. The indirect aim was to assess the role of such an intervention on adherence to a GFD. They were divided into two groups: those who received a dedicated 'Coeliac School' intervention (n=54) and those who received information in relation to CD at home (n=52). The intervention group underwent a 10-session educational programme. The primary outcome was psychological general well-being measured with a validated questionnaire. The intervention group showed psychological well-being at 10 weeks and that remained sustained after 3 months FU. Although a very thorough and time-consuming study, this intervention also is not applicable to all patients. In addition to that, the cohort is gender-biased and it is not clear how adherence to a GFD was measured. Furthermore, the clinical value of this intervention is questionable.

Role of improving education in increasing adherence to a GFD

In a US based study (n=75) Zabolotsky and colleagues (2017) assessed the role of an educational programme on CDAT and CDQoL and reported improvement in score post education but this was a short conference presentation and apart from passing mention about information on: the GFD, lifestyle changes, counselling for family members, and other associated conditions, details about the educational instruction and contents of the educational strategy were not available. In addition to that, CDAT was measured in non-conventional way i.e. increasing CDAT was linked with improved adherence. The information about this study are sparse and, although worth mentioning, cannot be considered a definitive intervention to increase adherence to a GFD.

Finally, there is also a report of an incomplete study, CD-DIET, which focused only on patients with CD and T1DM (Assor et al., 2015). The aim of the study was to evaluate the safety and efficacy of a GFD in patients with asymptomatic CD and T1DM with regards to diabetic control. However, one of the indirect aims was to develop rigorous guidelines to assess adherence and facilitate evaluation of a GFD on: metabolic control, bone health and patient quality of life in patients with CD and diabetes. The results of this study were not published.

Aims of the Research

This PhD aims to report factors influencing GFD adherence and whether there are any factors specific to people of SA origin with CD. From the information gathered, a subsequent study aims to improve GFD adherence in patients with CD through an intervention. The literature review above indicates that there remains a paucity of data on ethnic minority CD patients in the UK and the potential difficulties faced by this subset of the population in adhering to a GFD. Additionally, of substantial clinical importance, there is limited research on interventions to increase adherence to a GFD which are cost effective, acceptable to patients and above all not significantly technology dependant.

The PhD is divided in to three studies. Study I of this PhD thesis aims to establish the factors influencing GFD adherence in a cohort of Caucasians and SA residing in the UK. Study II, an interview based research study, aims to understand the factors influencing GFD adherence in Caucasian and SA patients residing in the UK who are not presently adhering to a GFD, and suggest interventions to help their adherence improve. Study III aims to improve GFD adherence in patients with CD currently not adhering to a GFD through an intervention, with a 6 month follow up (FU) period. The details of each of the three studies will be provided in the relevant chapters to avoid duplication of information. A summary is presented in the table below (Table No 12).

Table 12: Brief overview of the studies and their aims in relation to the PhD.

Study No/ Hypothesis	Aims
Study I: Adherence to a GFD may be measured through a combination of validated questionnaires	• To measure adherence to a GFD in relation to age, gender and ethnic background • Explore symptomatology in relation to activity of disease • Factors associated with adherence to a GFD
Study II: Adherence to a GFD is multifactorial and can be determined by questionnaires combined with telephonic interview	• To investigate reasons behind non-adherence to a GFD • To design an intervention for increasing adherence to a GFD
Study III: Interventions based on patients' input can increase adherence to a GFD	• To increase adherence to a GFD by an intervention • To evaluate the continuance of achieved adherence through FU

Chapter Two

Study I: An Investigation into Dietary Adherence of Patients with Coeliac Disease "No Triticeae"

SECTION I

Introduction

Research has shown that adherence to a GFD, which is challenging for a significant number of patients (Zarkadas et al., 2013), has multifactorial causes (Hall et al., 2009). A variety of methods including interviews and questionnaires has been used to determine the adherence and causes, but this area is still under researched. Improvement in adherence can not only reduce symptoms but may also reduce the long term complications of CD.

There is limited research in the area of GFD adherence in ethnic populations, especially in the UK. Most of the studies in this area are observational and cross sectional. This could be improved by including information from medical notes, clinical letters and computerised health records. This current study is a follow-up study of a pilot MSc project (LEVANT) (Muhammad, 2013) which studied 320 patients (67% female). The return rate was 57.6% (n=180) and the absolute adherence was 65% (116). There were no significant differences in adherence based on ethnicity, gender or age. The pilot study (Muhammad, 2013) proposed that a high power study should be conducted using the same database supplemented by medical notes. Additionally, linguistic support should be available to the ethnic minority patients in the cohort.

Study aim

The study aims to measure adherence to a GFD in relation to age, gender and ethnic background and explore symptomatology in relation to activity of disease along with factors associated with adherence to a GFD.

Method

This was a questionnaire based survey using validated instruments to evaluate basic demographics of CD and adherence to a GFD. Participants in this study were identified from the pathology database of

the University Hospitals of Leicester NHS Trust (UHL). The identified participants were approached via letter and sent a research pack through first class post. Return rate (RR) is defined as the number of completed units divided by the number of eligible units in the sample (Fan & Yan, 2010). Completed questionnaires were received, codified, entered and subsequently analysed. In addition, the medical records of the patients were screened for supplementary information. Informed consent was obtained from the patients who completed the questionnaire and returned it (Appendix 1.1c). The methodology was adapted from previously published studies (Butterworth et al., 2004, Leffler et al., 2007) and the MSc by the author (Muhammad, 2013).

Because of the potential volume of notes required and the difficulty associated with tracking them down, it was decided to use just the last 3 clinical letters from the computerised record, along with laboratory test results accessed using ILAB® or APEX®. Where it was felt necessary, if there was ambiguity in the clinical letters, notes were accessed for supplementary data. First of all the data was checked for associated comorbidity.

Design

The design of this observational study was cross sectional, as data was collected from a subset of the population at one specific point in time, using validated instruments i.e. two questionnaires and one food diary. In population based studies, cross sectional analysis is used to describe some feature of the population (Levin, 2006) and in this particular case it was used to collect information about: adherence to a GFD, causes behind low adherence and related issues (which are described below in the appropriate section).

Participants

The participants in this study came from the UHL pathology department database. The data had been coded by the computerised record system known as the Systematized Nomenclature of Medicine® (SNOMED). SNOMED uses a collection of medical terms (diseases in this context) and provides a reliable and consistent way to index, store and retrieve medical data in commonly used interfaces (in this case MS Excel® spreadsheets) (Cote & Robboy, 1980). Local approval to extract the data was obtained from the consultant pathologist, after approval of the ethics committee had been received. The record was then extracted by the pathology manager, who was kept blind to the purpose and aims of

the study in order to avoid any selection bias. Only adult patients diagnosed between 2004 and 2014 were selected for this study and they had to meet the diagnostic criteria of CD on pathological grounds as explained below. The geographic location of all the participants was Leicestershire, which is an English county in the Midlands. Demographic records were checked using the Trust's computerised diagnostic software, ILAB® (2nd Edition, 2010).

Inclusion criteria

All adult patients (18 years and above) diagnosed with CD on confirmed histological grounds between 2004 and 2014 in the SNOMED database of the department of pathology at UHL were selected for this study. In addition, for standardisation of diagnosis, only patients who were diagnosed by UHL pathologists were included. Moreover, for consistency in treatment and dietary advice received, only patients who were under the FU of UHL consultant gastroenterologists and dietitians were included in this study. Patient selection involved only those diagnosed with CD between 2004 and 2014.

Exclusion criteria

All patients below the age of 18 were excluded. In addition, all those who were not under UHL FU were excluded for ethical reasons, as the local Research and Development office approval was only applicable to UHL related patients and standardisation. Furthermore, patients with learning difficulties, those living outside Leicestershire and those who were diagnosed by non UHL pathologists were excluded from the study. Patients diagnosed with CD before 2004 were also excluded.

Materials/ instruments used

A total of three instruments were used to collect the data. In previous similar research (Muhammad, 2013) the questionnaire by Butterworth et al., (2004) was used and this time it was supplemented with a validated dietary adherence questionnaire (Leffler et al., 2009). The former questionnaire gathered epidemiological data and the latter only focused on adherence. Furthermore, a food diary (WCRF, 2013) was sent out to collect information about food and nutrient intake from the patients.

A postal invitation in the form of a research pack was then sent to all eligible patients. The research pack included an invitation letter (Appendix 1.1b), patient information sheet (Appendix 1.1a), study questionnaire (Appendix 1.1e-g), consent form (Appendix 1.1c), details for completing the study

questionnaires and a stamped addressed envelope. Demographic data was collected from the CD database at UHL; dietary adherence and quality of life related responses were extracted from the questionnaires.

Data analysis

Data was entered and analysed using SPSS V 24 (IBM SPSS Inc., Chicago, IL). Data was initially evaluated for characterization of the recruitment cohort in terms of: age range, gender distribution, ethnic variation and evidence for the diagnosis. To assess skewness, continuous variables e.g. age, were screened for normal distribution by using the Kolmogorov-Smirnov test and transformed if considered necessary. In addition to that, nonparametric tests such as $\chi 2$ test Mann-Whitney (MW) and Kruskal-Wallis tests were used to compare percentages. 2X2 contingency tables were used to compare nominal data in cross tabulation and the Odds Ratio (OR) was calculated. The Student's t-test or equivalent non parametric tests i.e. MWU test were used to analyse differences between the mean age and length of FU since diagnosis of the returnees and non-returnees of the questionnaire among the Caucasian and SA patients.

Binary Logistic Regression was used to find associations between certain parameters (membership of the Coeliac Society (CS), understanding food labels etc.) and adherence to a GFD. Logistic regression analysis provided a P value and an OR with a 95% confidence interval. For the purpose of this test and the study, all statistical values with a P value of <0.05 were considered significant.

Description of questionnaires used

The cognitive process to respond to a questionnaire involves four steps, namely: comprehension, recall, linking the retrieved information and communicating the response (Bowling, 2005). It is important that this process is facilitated by the design of the questionnaire and must have traits to reduce bias in this process. The questionnaires selected for this purpose, therefore, had general characteristics including: relevance to the area of interest (e.g. adherence in this case), reliability and validity (Roberts & Priest, 2006). The instruments selected had these properties and are described below.

A: Comprehension:

This is related to the respondents' ability to understand the question and be able to respond by following instructions (Lietz, 2010). It was noted that the questionnaire by Butterworth et al., (2004) did not have instructions for filling in the questionnaire and these were therefore added. All instruments had vocabulary which was appropriate for the target population (Brace, 2008) and the sentence structure was simple, without ambiguity or vagueness (Saris & Gallhofer, 2007, Aday & Cornelius, 2006). Furthermore, the questions were presented in a logical, sequential, tabulated and easy to follow manner, which aided visual comprehension of the document (Brace, 2008) .

B: Recall from Memory*:*

Significant sections of the instruments were concerned with recall, and that is the area which can be affected by recall bias (Brusco & Watts, 2015). Special care was therefore taken to screen the selected questionnaires for reducing recall bias (Eisenhower et al., 2004). For example, information about specific events (such as age of diagnosis) was cross checked with the medical record held in the hospital. It was noted that, instead of asking for a specific date, a temporal range was asked for, as that is easier to recall. Similarly, for better recall, patient selection involved only those diagnosed with CD in the past 10 years.

C: Response reporting*:*

It is generally accepted that information provided by the respondent is truthful, but care was taken not to make the questions too difficult, embarrassing or long; otherwise they may be difficult to answer and introduce social desirability bias (Holbrook & Krosnick, 2010). The questionnaires selected were screened for this and no socially unacceptable phrases or wordings were identified.

Butterworth et al., (2004) questionnaire

This questionnaire was selected because the population on which it had originally been used had similar geographical, social, ethnic and linguistic characteristics to our population (Butterworth et al., 2004). This questionnaire was originally used to survey Birmingham and the surrounding area of the Midlands; the population for this PhD was recruited from Leicestershire (East Midlands), where there is a large ethnic population with a similar demographic. For example, the ethnic populations of Birmingham and Leicester may be compared on the basis of their origin from South East Asia including: India, Pakistan, the Middle East, Bangladesh, Sri Lanka and Afghanistan (Birmingham City Council, 2018, Leicester City Council, 2018). Their languages include: Hindi, Urdu, Pashto, Punjabi, Persian, Dari and Arabic and the author can speak all of them (Appendix 1.1G). In addition to that, the questionnaire was focused on GFD adherence in Asian and Caucasian people, which is the area of interest for this study.

The questionnaire contained 20 questions and permission to use this questionnaire was obtained from the author of the study (Appendix 3.1). The questionnaire was designed to gather a variety of information including: symptoms before diagnosis, information given to the patients after diagnosis (by both physician and dietitian) and difficulties faced by them in following a GFD.

Clear instructions were added at the beginning of the questionnaire, in order to help the participants complete it. They were advised not to leave any part blank and instead write “Don’t know” or simply “DK.” Participants were also advised to use extra sheets if they felt it was necessary to add comments or extra information. The questionnaire was divided into several sections, with basic demographics such as age and gender included along with ethnicity details at the very start of the questionnaire. The next section included questions about dietary habits (vegetarian/ non-vegetarian) and information about their age at diagnosis. Following this, the time taken to arrive at a diagnosis was asked, to ascertain the gap between first contact with healthcare and diagnosis of CD. Thereafter, in the next section, all commonly known associated symptoms of CD were listed and patients were asked to tick those applicable to them. Symptoms in this section were related both to GI tract symptoms (like diarrhoea, abdominal pain, bloating and oral ulceration) and extra-intestinal symptoms (like rash, weight loss, hair loss and generalised fatigue). There was also an area where participants could state if they were in fact asymptomatic (and had been diagnosed due to a positive family history for CD). Information given to the patients by both physicians and dietitians was explored next. This included questions on the

information they had received about the disease and disease process, any FU plan and instructions about a GFD and its importance. Patients were also asked about their satisfaction with the information given to them, by both physicians and dietitians and they were encouraged to write down the reasons if they were not satisfied. One question specifically asked about the role of dietitians in the management of CD.

The next few questions investigated the difficulties faced by the patients in following a GFD. This included their baseline understanding and perception of a GFD and if they were symptomatic after dietary transgressions. The economic aspects related to following a GFD were also explored and they was asked if they were aware that some GFP are available on prescription. Relevant to this question at the time of this research, health commissioners in many NHS English CCGs were restricting the dispensing of GFP on prescription. In the East Leicestershire and Rutland CCG, these changes have now been implemented and only eight items are allowed on prescription, with a plan to review the items in 12 months (East Leicestershire and Rutland CCG, 2016).The last few questions were about Coeliac UK (CUK) and participants were asked if they were members of CUK; reasons behind non-membership were explored. The participants were also asked if they would be happy to be contacted in the future for similar studies.

Leffler et al., (2009) questionnaire

This validated questionnaire was selected for its ability to indicate dietary adherence to a GFD. It had also been used in recent similar studies (Nazareth et al., 2015, Sainsbury et al., 2013b, Villafuerte-Galvez et al., 2015, Mahadev et al., 2013). The seven item questionnaire was considered appropriate to minimise participant burden and promote a good response rate (Iglesias & Torgerson, 2000). Permission to use this questionnaire was obtained from the author of the study (Appendix 3.2).

The questionnaire utilised a five point Likert scale (Likert, 1932) and explored general symptoms associated with low adherence, such as headache and low energy. This was followed by two questions asking about personality traits such as self-discipline (by exploring participants' ability to follow a GFD in non-familiar environments such as restaurants) and a cautious nature (when considering consequences of actions). Next a specific question was asked about self-assessment and patients' views were invited. Furthermore, the questionnaire asked specific questions about the frequency of

gluten ingestion, including if there had been no ingestion in the past four weeks. The questionnaire had the added advantage of being easily translated into different languages and could be administered over the telephone because of its simple structure. Last but not least, the questionnaire generated continuous data which was easy to code and analyse in statistical operations.

WCRF food diary

Food diary analysis was completed by CD patients adhering to a GFD to assess their nutritional status (Shepherd & Gibson, 2013), but reliable adult studies with good power in non-adherent patients are lacking. This study utilised a 3 days World Cancer Research Fund (WCRF) food diary to explore unintentional gluten ingestion (WCRF, 2013). This was a short and easily understandable diary with one page per day (Appendix 1.1F).

Ethics

Integrated Research Application System (IRAS) was used to apply for ethical approval for the study (IRAS ID: 159160). The study was first approved by the University of Roehampton Ethics Committee (LCS 14/112). Thereafter, ethical approval was applied for through the central Research and Ethics Committee (REC) and permission was granted from the REC NHS London – Queen Square (Ref: 14/LO/2128). The local NHS research and development department at UHL was involved through a site specific application form linked to IRAS (UHL Ref: 11418). The ethical approval letters from the relevant bodies for this study are attached in the appendix section (Appendices 2.1A-C).

Procedure

Each participant was given a unique trial number, which was assigned by the principal investigator to preserve the confidentiality of the patients. This was stamped on every document using a COLOP® mini-folio (S126) prefilled number generating stamp. Assurance regarding the confidentiality was clearly stated in the invitation letter and patients were encouraged to clarify any concerns (if they had any) by either writing to the researchers or telephoning them at a particular time (Wednesday afternoon). Contact details for independent information were also provided.

During the recruitment phase of the study, extreme care was taken to preserve the confidentiality of the patients by constructing a comprehensive password protected database. The database was received from the pathology laboratory using the UHL email and only Trust specified memory sticks were used. Data was accessed on a need to know basis only. The researcher analysed the diagnostic database and only relevant details like: age, sex, and ethnicity, basic information given at the first meeting with a dietitian and histological confirmation were entered into the database. Only then were the questionnaires sent out.

The first phase of the study was the postal recruitment, where patients were identified by their pre-allocated number. The suitably identified patients were carefully re-evaluated prior to sending the research pack out, as a precautionary measure to comply with the exclusion criteria and prevent sending out the research pack to unintended recipients (e.g. minors, learning disabled or deceased patients). Additional information gained from the CD database like age, ethnicity and gender was also entered onto the research database.

The returned questionnaire was kept in a separate file in the research room at UHL and all identifiable data was kept linked only to trial numbers to protect confidentiality. Each response on the questionnaire was coded from 0 to 12.

Conduct of the study

No adverse incidents were reported. Patients were provided with contact information for the Head of Department, in case they had any issues, queries or questions. One patient had an issue regarding the way she was approached for the study i.e. how did we obtain her contact details? This was duly discussed with the university and academic supervisors. Full explanation was given about the ethical procedure, methodology of patient contact and patient comments were invited; she was satisfied with the explanation. Thereafter, no further contact was received from the patient.

A separate leaflet in seven ethnic languages accompanied the invitation letter to invite questions from anybody who had difficulty understanding the purpose or conduct of the study, even if English was not their first language (Appendix. 1.1G). The researcher received a total of 13 calls from different patients, all enquiring about different aspects of the study. The calls could be broadly grouped into 4 themes. Firstly, 4 calls were received enquiring about confidentiality issues. Strong reassurance was given about

our adherence to confidentiality guidelines during collection, storage and safe disposal of identifiable data before, during and after the study. All of those who enquired were satisfied with the explanation given. Secondly, 3 callers had specific questions about the purpose of the research. They were given full explanations about the aims and purpose of the research. Thirdly, 3 callers pointed out mistakes in the questionnaires, especially question number 2, where ethnicity was confused with religion; the researcher apologized. Finally there was a caller who asked for different questions to be explained to them in their language, which was done.

Data entry:

In the first stage, the entered data was checked for any errors and missing data. The researcher found cases (n=4) where typographical errors were detected and a further two cases where data was missing. Missing data was cross checked with the paper based data and the missing values were rectified. Following this, in the second stage, coding of the data was cross verified, and no coding errors were identified. All entries in the software were done by the researcher (author) and 20% of the data was double checked for accuracy by an audit committee in 2 steps. The committee suggested changes to a few entries and, after rectifying the data errors, data was statistically analysed. No omission in the data was left blank. Ambiguous phrases such as ‘not available’ were avoided. No patients withdrew from the study, although it was clarified with the patients that they were allowed to withdraw from the study at any time without being questioned about the reasons.

SECTION II

Results

A total of 1,248 patients were identified from the CD database at UHL. The pathology database (SNOMED®) has extensive records for CD patients (over 2000); only those patients who were diagnosed between January 1st 2004 and December 1st 2014 were selected (11 years). Data was broken down into diagnosis of CD per year and the average number of patients diagnosed per year was 111. Additionally there was a trend of increasing numbers of CD cases being diagnosed over the years. The number of diagnosed cases of CD per year is shown in the bar chart below (Figure No 7).

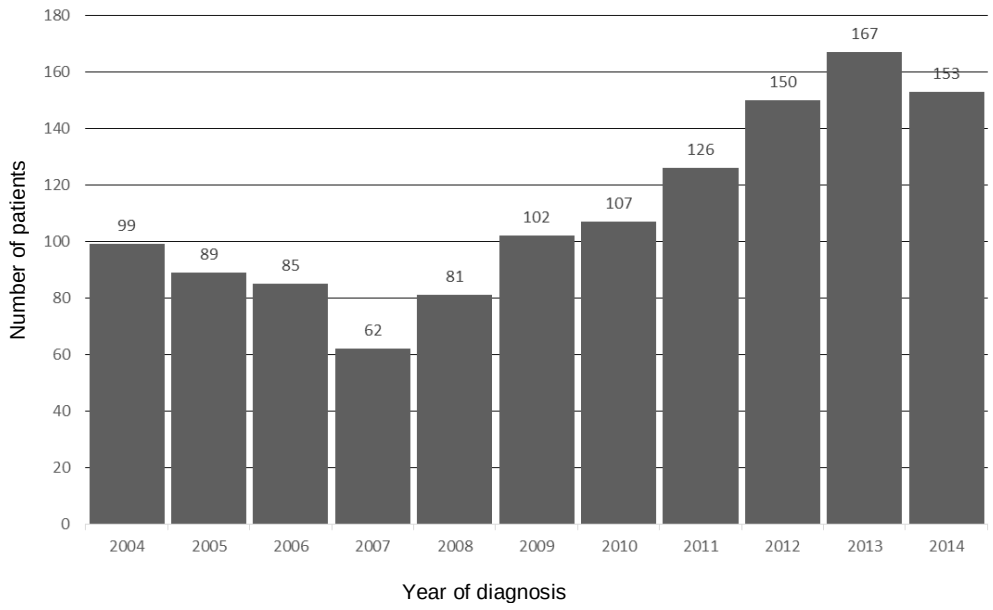

Figure 7: The diagnoses of CD per year at UHL

The selected population had objectively confirmed histological changes in their duodenum consistent with CD.

Diagnosis of CD in the study population

Data was extracted using SNOMED®, a coding system devised by the College of American Pathologists as explained above. Pathological reports of those who responded to the questionnaire were manually read and features of lymphocytosis (with or without crypt shortening or distortion) were confirmed.

Furthermore, for correct diagnosis, it was ensured that all those with histo-pathological appearances of CD had corresponding supportive positive serology (either anti-tTG or endomysial anti-bodies) at some stage during their diagnosis or FU. Thus the diagnoses were established by a combination of pathological and serological features.

Study population

SNOMED® data generated 1,248 patients and, after applying the exclusion criteria, 972 were selected for the postal questionnaire. Out of the excluded patients, 170 were minors and 33 were duplications of data. A further 73 patients were excluded after applying exclusion criteria such as: patients moved out of geographic region (n=47), doubtful diagnosis (n=11), death of patients (n=4), no address available (n=4) and learning difficulty (n=2). The final excluded category (n=5) had no active FU with the department and no GP details were available, so it was assumed that they were either lost to FU or they were not on a GFD. Another possibility is that they were from outside the Leicestershire area and were only diagnosed at UHL and were not receiving FU there. It is also possible that a few of them did have active CD and needed a GFD, but were diagnosed by non GI physicians and were awaiting gastroenterologist input in their management or they had been referred for a second opinion from outside the Leicestershire region.

Age, gender and ethnicity of the study population

The mean age for the population (n=972) ranged from 18 to 85 years (Mdn = 50, IQR = 35-65) and it was not distributed normally ($p<0.01$), with skewness of -.02 (SE = .07) and kurtosis of -1.03 (SE = .15). The most prevalent group was the age ranging between 34 to 50 years followed by 51 to 60 years. The sample was predominantly female (67.7%), compared to 32.3% males; the females had a slightly lower mean age. Female age ranged from 18 to 83 years (Mdn = 50, IQR = 34-65) and was not distributed normally ($p<0.01$), with skewness of .01 (SE = .09) and kurtosis of -1.06 (SE = .19). The age for males ranged from 18 to 85 years (Mdn = 51, IQR = 38-66) and was also not distributed normally ($p=0.03$), with skewness of -.08 (SE = .13) and kurtosis of -.93 (SE = .27). There was no significant difference between the ages of males and females; the Mann-Whitney U (MWU) test was used: males (Mdn = 51.5, n = 314) and females (Mdn = 49.5, n = 658), U = 98029, z = -1.28, p = .197, r = -.04 (Appendix 4.1Ac). Ethnic analysis showed that there were 829 (85.3%) Caucasians and the remaining 143 (14.7%) were SA, which included: Indian, Pakistani, Bangladeshi and Afghani populations. On the basis of

gender, the Caucasian population could be further divided into 573 (64%) females and 256 (28.6%) males. Similarly, there were 85 (59.4%) females and 58 (40.5%) males in the SA group. Out of the SA population, 64 (44.7%) identified themselves as Hindu, 42 (30.6%) as Sikh and 37 (25.8%) as Muslim. The table below shows the breakdown of the entire study population from the database (Table No 13)

Table 13: Characteristics of the entire study population from the CD database.

		Gender		P Value
	Total (n=972)	Male (n=314)	Female (n=658)	
Median Age (IQR)	50.0 (35-65)	51 (38-66)	50 (34-65)	0.19**
Age Groups				**0.05*** **
< 20 years	38 (3.9%)	11 (3.5%)	27 (4.1%)	
21-30 years	138 (14.2%)	39 (12.4%)	99 (15%)	
31-40 years	131 (13.5%)	40 (12.7%)	91 (13.8%)	
41-50 years	183 (18.8%)	62 (19.7%)	121 (18.4%)	
51-60 years	181 (18.6%)	62 (19.7%)	119 (18.1%)	
61-70 years	155 (15.9%)	49 (15.6%)	106 (16.1%)	
> 70 years	146 (15%)	51 (16.2%)	95 (14.4%)	
Ethnicity				**0.02*** **
White Caucasians	829 (85.3%)	256 (81.5%)	573 (87.7%)	
South Asians	43 (14.7%)	58 (18.5%)	85 (12.9%)	
Ethnic groups				**<0.01*** **
Sikh	42 (4.3%)	24 (7.6%)	18 (2.7%)	
Muslim	37 (3.8%)	13 (4.1%)	24 (3.6%)	
Hindu	64 (6.6%)	21 (6.7%)	43 (6.5%)	

***IQR Interquartile range **MWU test ***Chi Square test**

The Table above shows that there were significant differences between genders in terms of ethnicity and age groups, but there was no significant difference between the median ages of males and females (Appendices 4.1Aa-f).

Return rate of questionnaire

A total of 375 completed questionnaires were received, which gives a RR of 38.6%. None of the questionnaires was left blank and the information was legible. Out of 375 completed questionnaires, 63 (16.8%) had additional comments which had 5 different themes and these are explained in the relevant

sections. For simplicity, the entire population was divided into questionnaire responders (n=375), who will make up the study population, and non-responders (n=597).

Age of the study population

The mean age for those who returned the questionnaire (n=375) ranged from 18 to 85 years (Mdn = 50, IQR= 33-60) and was not distributed normally ($p<0.01$), with skewness of .01 (SE = .12) and kurtosis of -.91 (SE = .25). The age of non-responders (n=597) ranged from 18 to 83 years (Mdn = 51, IQR= 37-67) and was not distributed normally ($p<0.01$), with skewness of -.04 (SE = .10) and kurtosis of -1.10 (SE = .20). The most prevalent responder age group was 41 to 50 years of age (19%), whereas among non-responders this was 51 to 61 years (24%). There was a significant difference between the ages of responders (Mdn = 50, n = 375) and non-responders (Mdn = 51, n = 597), U = 100469, z = -2.69, $p<0.01$, r = -.17 (Appendix 4.1Bc). This result suggests that advancing age was linked to a lower RR for the questionnaire (Table 2).

Ethnic diversity of the study population

In the responder group (n=375), White Caucasian was the dominant ethnicity: 337 (90%) of the patients were White Caucasians and 38 (10%) were SA. Equally, in the non-responder group (n=597), White Caucasian was the dominant ethnicity: 492 (82.4%) of the patients were Caucasians and the remaining 105 (17.6%) were SA. The SA population in the responder group (n=38) had two (5%) Sikh males and 18 (47%) Sikh females. Similarly, the number of Muslim males was three (7%) and 6 (14%) were females. Additionally, the number of Hindu males was 5 (13%) and females was 4 (10.5%). The SA in the non-responders group were further divided into sub-groups and it showed that 20 (52.6%) identified themselves as Sikh, 9 (23.6%) as Hindu and 9 (23.6%) as Muslim. Chi-square for independence indicated that there was a significant association between ethnicity and questionnaire RR, $\chi 2$ (1, n=972) = 10.201, $p<0.01$, phi = -.102 (Appendix 4.1Be). The data revealed that White ethnic patients (40.7%) had a higher completion rate than patients of South Asian ethnicity (26.6%).

Gender of the study population

Out of 375 responders, 267 (71.2%) were females and the remaining 108 (28.8%) were male. From an ethnic point of view, of the 337 Caucasians who responded, 239 (70.9%) were female and 98 (29.1%) were males. Similarly, among the 38 Asian responders, 28 (73.7%) were female and the remainder were

males (26.3%). The completion rate for the female group was 40.5% and that of the male group was 34.3% (a trend towards a significant association p=0.06; Table No 14). (Appendices. 4.1Ba-f).

Table 14: Characteristics of the study population from the CD database.

Variables	N (Total)	Response status		*P* Value
		Responders	Non-responders	
	972	375 (38.6%)	597 (61.4%)	
Median Age (IQR)	50 (35-65)	50 (33-60)	51 (37-67)	**<0.01***
Age Groups				**<0.01****
< 20 years	38 (3.9%)	24 (6.4%)	14 (2.3%)	
21-30 years	138 (14.2%)	59 (15.7%)	79 (13.2%)	
30-40 years	131 (13.5%)	42 (11.2%)	89 (14.9%)	
41-50 years	183 (18.8%)	69 (18.4%)	114 (18.4%)	
51-60 years	181 (18.6%)	91 (24.3%)	90 (15.1%)	
61-70 years	155 (15.9%)	48 (12.8%)	107 (17.9%)	
> 70 years	146 (15%)	42 (11.2%)	104 (17.4%)	
Gender				0.06**
Male	314 (32.2%)	108 (28.8%)	206 (34.5%)	
Female	658 (67.7%)	267 (71.2)	391 (65.5%)	
Ethnicity				**<0.01****
White Caucasians	829 (85.3%)	337 (89.9%)	492 (82.4%)	
South Asians	143 (14.7%)	38 (10.1%)	105 (17.6%)	
Ethnic groups				
Sikh	42 (4.3%)	20 (5.3%)	22 (3.7%)	
Muslim	37 (3.8%)	9 (2.4%)	28 (4.7%)	
Hindu	64 (6.6%)	9 (2.4%)	55 (9.2%)	

***MWU test **Chi Square test**

Dietary preferences, health problems in childhood and age at diagnosis*:*

Of the 375 participants who returned the questionnaire, 15 (4%) were vegetarian and the rest were non-vegetarian. There was a dominance of Asians patients in the vegetarian category 11/15 (73%); seven were Hindus and four were Sikhs. Only four Caucasians reported being vegetarian. None of the Muslim participants identified themselves as vegetarian. Eighty-one participants (30%) reported a childhood

related health problem and the majority of them (66.6%) were female, however a χ2 analysis revealed no difference between males and females (1, n=375) = 1.035, p=.30, phi = -.053) (Appendix 4.1Cb). Similarly, age at diagnosis was explored and the majority of patients (26%) were diagnosed between ages 18 -30 and there was a female predominance (79%) in this group. Additionally, a second peak is observed between ages 51-60 with a male majority (30.6%). (Appendices 4.1Ca-c)

Symptoms at diagnosis and types of coelaic disease

The most common symptom at diagnosis was fatigue (61.6%), followed by stomach pain (55.5%), bloating (38.8%) and diarrhoea (35%). The symptoms are shown in the Table below (Figure No 8).

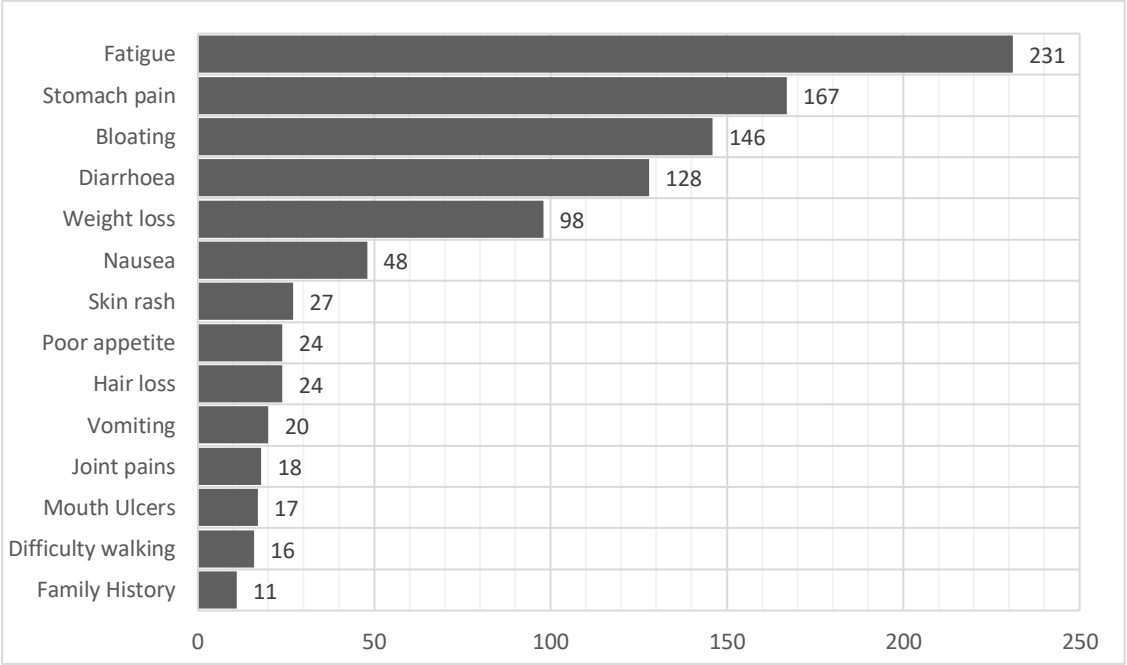

Figure 8: Symptoms of CD reported at diagnosis.

Fatigue, bloating and diarrhoea were the most common symptoms in females; among males the most common symptoms were fatigue and weight loss. Stomach pain, hair loss and fatigue were the most common symptoms among Asians. Symptoms were further analysed according to the gender and the difference was significant between male and females when reporting fatigue (1, n=375) = 6.09, p=.014, phi = -.12) (Appendix 4.1CD1) and nausea (1, n=375) = 5.42, p=.02, phi = -.12) (Appendix 4.1Cd8). This means that female gender were reporting more fatigue and nausea as compared to male.

Table 15: Number of participants reporting CD symptoms at diagnosis split by ethnicity and gender (% of total (n=375) count).

	Ethnicity			**Gender**		
Category	White (n=337)	Asian (n=38)	*p*	Male (n=108)	Female (n=267)	*p*
Childhood symptoms	73 (19.5%)	8 (2.1%)	0.931	27 (7.2%)	54 (14.4%)	0.30
Fatigue	211 (56.3%)	20 (5.3%)	0.23	**56** (14.9%)	**175** (46.7%)	**0.01**
Hair loss	24 (6.4%)	0 (-- %)	0.08	6 (1.6%)	18 (4.8%)	0.65
Stomach pain	**157** (41.9%)	**10** (2.7%)	**0.01**	45 (12%)	122 (32.5%)	0.47
Bloating	128 (34.1%)	18 (4.8%)	0.26	38 (10%)	108(29%)	0.34
Skin rash	24 (6.4%)	3 (0.8%)	0.86	6 (1.6%)	21 (5.6%)	0.43
Poor appetite	22 (5.9%)	2 (0.5%)	0.76	7 (1.9%)	17 (4.5%)	0.96
Diarrhoea	119 (31.7%)	9 (2.4%)	0.15	32 (8.5%)	96 (25.6%)	0.24
Nausea	44 (11.7%)	4 (1%)	0.65	**7** (1.9%)	**141** (11%)	**0.02**
Vomiting	**15** (4%)	**5** (1.3%)	**0.02**	4 (1%)	16 (4.3%)	0.37
Aphthous ulcers	15 (4%)	2 (0.5%)	0.82	4 (1%)	13 (3.5%)	0.62
Weight loss	92 (24%)	6 (1.6%)	0.12	26 (6.9%)	72 (19.2%)	0.56
Family history	16 (4.3%)	2 (0.5%)	0.88	5 (1.3%)	13 (3.5%)	0.92
Joint pain	16 (4.3%)	2 (0.5%)	0.88	4 (1%)	14 (3.7%)	0.52
Difficulty walking	15 (4%)	1 (0.3%)	0.59	3 (0.8%)	13 (3.5%)	0.36

The largest group of patients (28.5%) was diagnosed between 6 to 12 months after the appearance of symptoms. A minority of the patients (3.4%) never had any symptoms and were placed in the “No symptom” group. A Pearson chi-square for independence indicated no significant association between gender and time taken to diagnose, $\chi 2$ (1, n=375) =.718, p=.94, phi = -.044 (Appendix 4.1Cf). Nor was there a significant association between ethnicity and time taken to diagnose, $\chi 2$ (1, n=375) = 7.70, p=.10,

phi = .143 (Appendix 4.1Cf). It is thus concluded that time taken to diagnose CD was not biased by either gender or ethnicity.

The presentation of CD was further categorised based on the presence of typical classical, non-classical or atypical symptomatology; patients were divided into three groups, termed as: “Classical”, “Non-Classical” and “Subclinical” disease respectively. There was female predominance in all groups. Sixty percent of participants in the Non-Classical group were female, 35% in the Classical and 4.5% in the Subclinical group (Appendix 4.1Ce).

Appointment with hospital physician and dietitian

Clinical appointment with hospital doctor

Among the responders (n=375) a clear majority (80% (n=303)) of the patients reported having received information about the diagnosis. Similarly, 335 (89%) reported that they were advised to follow a GFD and 345 (92%) of them were referred to a dietitian. Eighty five patients (23%) wrote comments in the "other" section and these responses had 4 main themes. Firstly, 40 out of 85 (47%) were praising the clinical service. Secondly, 16 (19%) were referring to appointment delay, cancellation and waiting time in the hospital. Thirdly, 20 patients (34%) commented regarding access to the clinic such as: hospital parking, lack of directions to the clinic and lack of flexibility for clinical appointments. Nine participants made miscellaneous comments which were not relevant to the question. Overall dissatisfaction with clinician service was 4% (n=18). Multiple reasons were given by Caucasians to account for dissatisfaction and there was no main theme. They included: poor explanation by the doctor (7), no chance was given for questions at the end of the clinical session (7), the session was rushed (10), use of medical jargon (3), poor eye contact (7) and doctor was writing and ignored my questions (6). Asian patients on the other hand reported no dissatisfaction with the service at all (Appendices 4.1Da-g).

Clinical appointment with hospital dietitian

All patients answered the question related to the information given by the dietitian. The majority agreed that an information pack containing a diet sheet, food list and starter pack was provided. Satisfaction with the dietitian was 92% (n=345) and all of those who were dissatisfied were Caucasian. Only 15 participants entered comments and there were 2 main themes. 6 patients wanted another session with the dietitian and 3 pointed out that a local website from the hospital could help to resolve their issue. 158 patients (87%) recognized the role of the dietitian in the management of CD. The table below compares these appointments in relation to gender and ethnicity of the responders. (Table No 16) (Appendices 4.1Dg-p).

Table 16: Comparison of appointments with dietitian and doctor.

	Gender			Ethnicity		
	Male n=108	Female n=267	P	White n=337	Asian n=38	P
Clinical appointment with Clinician						
Explained what CD was	93 (86%)	210 (78%)	0.09	269 (80%)	34 (89%)	0.15
Told me to follow a GFD	99 (92%)	236 (88%)	0.35	302 (87%)	33 (87%)	0.60
Referred me to a dietitian	103 (95%)	242 (91%)	0.35	309 (92%)	36 (95%)	0.51
Arranged a follow up	90 (83%)	222 (83%)	0.96	227 (88%)	35 (92%)	0.12
Gave me information about CD	94 (87%)	224 (84%)	0.44	286 (85%)	32 (84%)	0.91
Satisfaction with the information	105 (97%)	252 (94%)	0.24	320 (95%)	37 (97%)	0.50
Appointment with dietitian						
Explained the diagnosis and GFD	103 (95%)	242 (91%)	0.12	309 (92%)	36 (93%)	0.51
Discussed GFD	100 (93%)	250 (94%)	0.71	312 (93%)	38 (100%)	0.08
Discussed Coeliac Society UK	102 (94%)	250 (94%)	0.76	314 (93%)	38 (100%)	0.09
Information pack provided	101 (93%)	255 (95%)	0.42	318 (94%)	38 (100%)	0.13
Discussed prescription of GFP	98 (91%)	243 (91%)	0.93	303 (89%)	38 (100%)	**0.04**
Arranged a follow up	94 (87%)	232 (86%)	0.97	288 (85%)	38 (100%)	**0.01**
Contact number given	91 (84%)	221 (83%)	0.72	275 (82%)	37 (97%)	**0.01**
Does dietitian have a role in CD	98 (91%)	229 (86%)	0.49	289 (85%)	38 (100%)	**0.01**
Satisfaction with the information	101 (93%)	244 (91%)	0.19	307 (89%)	38 (100%)	**0.05**

Data displayed here are returners who answered yes to the questions

Significant differences were noted in the perceptions of Asians and Caucasians in relation to the dietitian appointment. For example, Asians were more informed in relation to: prescriptions, arrangement of FU, having a dedicated contact number given to them and satisfaction with the information given (Appendices 4.1Dj-o).

CD from the patient's perspective and adherence to a GFD

All patients who returned the questionnaire (n=375) provided information about adherence to a GFD. They were divided into two groups: adherent and non-adherent. In the adherent group, which showed complete abstinence from gluten, there were 228 (60.8%) patients and the remaining 39.2% were non adherent based on the frequency of ingestion of gluten (monthly, weekly or daily) in their diet. They were further divided into 3 main categories: mild non-adherence, moderate and severe non-adherence groups who ingested gluten: once a month, once a week and daily respectively. The relative frequencies of each group are shown below in the bar chart (Figure No 9).

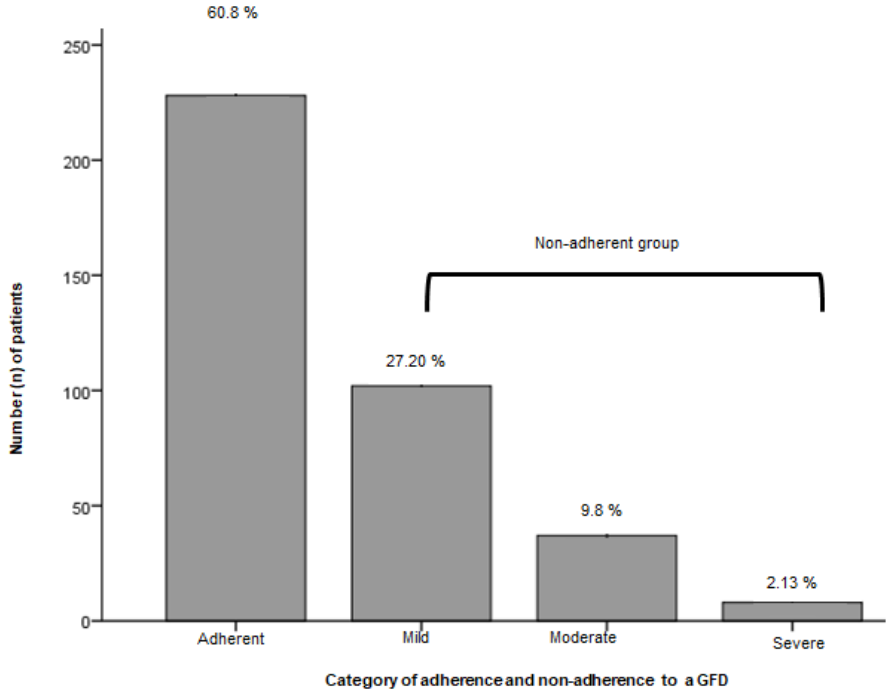

Figure 9: Categories based on frequency of gluten ingestion. Mild=once a month, Moderate =once a week, Severe =daily.

In the adherent group (n=228) there were 63 males (27%) and 165 females (73%). Similarly, the non-adherent group contained 45 males (30%) and 102 females (70%). A Pearson chi-square for independence indicated no significant association between gender and dietary adherence, $\chi 2$ (1, n=375) =.387, p=.53, phi = -.032. It is noteworthy that all those in the severely non-adherent group were female (n=8) (Appendix 4.1Ea). Based on ethnicity, in the absolutely adherent group (n=228) there were 206 (90%) Caucasians and 22 (10%) SA and a Pearson chi-square for independence indicated no significant association between ethnicity and dietary adherence, $\chi 2$ (1, n=375) =.150, p=.69, phi = -.020 (Appendix

4.1Eb). The ages of patients who were absolutely adherent to a GFD (n=228) ranged from 18 to 82 years; data was not distributed normally ($p<0.01$), with skewness of -.03 (SE = .12) and kurtosis of -.96 (SE = .32). In both the adherent (23.8%) and non-adherent groups (24%) the most prevalent age-group was between 51 and 60 years of age. The ages of the adherent group (Mdn = 51, n = 228) were not significantly greater than those of the non-adherent group (Mdn = 51, n = 147), as indicated by the MWU test, U = 15911, z = -.827, p = .40, r = -.04 patients. The results of the demographics have been summarised in the Table below (Table No 17) (Appendix 4.1Ec1).

Table 17: Table 6: Comparison of adherent (absolute) and non-adherent groups.

		Adherence to a GFD		
Variables	**N (Total)**	**Adherent**	**Non-adherent**	***P* Value**
	375	228 (60.8%)	147 (39.2%)	
Median Age (IQR)	50 (33-60)	51 (33-61)	48 (33-59)	0.40*
Age Groups				
< 20 years	24 (6.4%)	12 (5.3%)	12 (8.2%)	
21-30 years	59 (15.7%)	37 (16.2%)	22 (15%)	
30-40 years	42 (11.2%)	25 (11%)	17 (11.6%)	
41-50 years	69 (18.4%)	39 (17.14%)	30 (20.4%)	
51-60 years	91 (24.3%)	56 (24.6%)	35 (23.8%)	
61-70 years	48 (12.8%)	34 (14.9%)	14 (9.5%)	
> 70 years	42 (11.2%)	25 (11%)	17 (11.6%)	
Gender				0.53**
Male	314 (32.2%)	108 (28.8%)	45 (30.6%)	
Female	658 (67.7%)	267 (71.2%)	102 (69.4%)	
Ethnicity				0.69**
White Caucasians	337 (89.9%)	206 (90.4%)	131 (89.1%)	
South Asians	38 (10.1%)	22 (9.6%)	16 (10.9%)	
Sikh	20 (5.3%)	11 (4.8%)	9 (6.1%)	
Muslim	9 (2.4%)	6 (2.6%)	3 (2%)	
Hindu	9 (2.4%)	5 (2.2%)	4 (2.7%)	

***MWU test **Chi Square test, IQR= Interquartile range.**

In summary, the adherence rate to a GFD is 60.8% and it is not affected by advancing age, ethnicity or gender.

Difficulties faced in following a GFD and symptoms post gluten ingestion

Patients experienced difficulty in adhering to a GFD. For example, 301 (80%) agreed with the statement 'gluten free products (GFP) were expensive' and 284 (76%) were not happy with the amount of GFF their GP was prescribing for them. Of the 278 (74%) patients who were able to get GFP on prescription, only 218 (58%) agreed that they were getting sufficient. Additionally, several statements in the questioannire were analysed in relation to adherence to a GFD. Prescription of gluten free product on prescription was associated significantly with adherence to a GFD: $\chi 2$ (1, n=375) =16.8, p <0.01, phi = .21 (Appendix 4.1Fa). Additionally, understanding of gluten free food ($\chi 2$ (1, n=375) =6.49, p =0.01, phi = -.13 (Appendix 4.1Fa), amount of GFP on prescription ($\chi 2$ (1, n=375) =5.69, p <0.01, phi = -.12 (Appendix 4.1Fc) and understanding of food labelling ($\chi 2$ (1, n=375) =20.29, p <0.01, phi = -.23 (Appendix 4.1Fe) were also associated with adherence to a GFD. It means that those who were receiving either no or less GFP from the GP, those who were not able to understand food labelling and those who did not know which food to eat were significantly less adherent to a GFD (Appendices 4.1Fa-g). These statements were also analysed according to gender and ethnicity and the results are displayed I the table below (Table No 18) (Appendices 4.1Ga-g and 41.H a-g).

Table 18: Difficulties reported by patients not adhering to the gluten free diet (n=147) comparing ethnicity and gender

	Adherent to GFD					Gender					Ethnicity				
	Adherent		Non-adherent			Male		Female			Asian		White		
	n=228 (60.8%)		n=147(39.2%)			n=108 (28.8%)		n=267 (71.2%)			(n=38, 10%)		(n=337, 90%)		
	Yes	No	Yes	No	*P**	Yes	No	Yes	No	*P**	Yes	No	Yes	No	*P**
1	186 (82%)	42 (18%)	92 (63%)	55 (37%)	**<0.01**	82 (76%)	26 (24%)	196 (73%)	71 (27%)	0.64	34 (89%)	4 (11%)	244 (72%)	93 (28%)	**0.02**
2	19 (9%)	209 (91%)	25 (17%)	122 (83%)	**0.01**	9 (8%)	99 (92%)	35 (13%)	232 (87%)	0.19	29 (76%)	9 (24%)	15 (4%)	322 (96%)	**<0.01**
3	14 (6%)	214 (94%)	12(8%)	135 (92%)	0.45	4 (4%)	104 (96%)	22 (8%)	245 (92%)	0.11	1 (3%)	37(97%)	25 (7%)	312(93%)	0.27
4	163 (71%)	65 (29%)	121 (82%)	26 (18%)	**0.01**	83 (77%)	25 (23%)	201 (75%)	66 (25%)	0.74	36 (95%)	2 (5%)	248 (74%)	89 (26%)	**0.04**
5	8 (4%)	220 (96%)	26 (17%)	122 (83%)	**<0.01**	12 (11%)	96 (89%)	21 (8%)	246 (92%)	0.31	20(53%)	18 (47%)	13 (9%)	324 (91%)	**<0.01**
6	189 (83%)	39(17%)	112 (76%)	35 (24%)	0.11	82 (76%)	26 (24%)	219 (82%)	48 (18%)	0.17	37(97%)	1 (3%)	264 (78%)	73 (22%)	**0.05**
7	130 (57%)	98 (43%)	93 (63%)	54 (37%)	0.22	63 (58%)	45 (42%)	160 (60%)	107 (40%)	0.77	31 (82%)	7 (18%)	192(57%)	145 (43%)	**0.03**

***Chi Square test.** Numbers on the left represent statements: **Statement 1:** Do you get GF food on prescription, **Statement 2:** I don't understand what to eat, **Statement 3**; I don't have time to prepare meal, **Statement 4:** My GP does not prescribe enough **GFP Statement 5:** I don't understand food labelling **Statement 6:** GF diet is expensive **Statement 7:** GF diet is unpleasant

It is clear from the table above that there are significant differences between South Asians and white Caucasians in response to all statements except “I don’t have time to prepare meals”. Symptoms post gluten ingestion were explored next and out of the 147 non-adherent patients, only 87 reported symptoms on introducing gluten. Abdominal pain was reported by 72 (19%), fatigue by 73 (19%) and diarrhoea by 42 (14.4%). (Appendix 4.1I)

Membership of the Coeliac Society and availability of GFP on prescription

The question about the CS was completed by all participants. Although 352 (93%) responded that they were told about the CS in their consultation with the dietitian, only 202 (53) joined the CS (186 Caucasians and 16 Asians; Chi Square test p= 0.125). Those who were not members of the CS (n=173) had variable reasons. Eighty three participants (48%) reported they did not feel it was important to be a member of the CS, whereas 53 patients (38.6%) cited other reasons such as: expense related to membership, confidentiality issues, fear that their address might be used for junk mail and others stated that they would think about it. Membership of Coelaic UK was strongly associated with better adherence to a GFD ($\chi 2$ (1, n=375) =15.4, p <0.01, phi = .20 (Appendix 4.1Ih).

Adherence was further analysed by entering it into Binary Logistic regression. Presence (1) or absence (0) of adherence was entered for different variables such as: membership of the CS, understanding of food labelling, affordability of GFP, obtaining GFP on prescription and obtaining enough GFP on prescription. This generated an OR and p values for individual factors. Results are summarised in Table below (Table No 19).

Table 19: Combined results of the 2X2 Contingency table and χ2 test in comparison of different factors.

	Responders (n=375)						
Different factors/ Statements which may be related to non-adherence to a GFD	**Adherent %**		**Non-adherent %**				
	Yes	**No**	**Yes**	**No**	**OR**	**95% CI**	**p Value**
Are you a member of the Coeliac Society	32	28.8	12.5	26.7	2.09	1.33 - 3.7	**<0.01**
GFD is unpleasant	34.4	26.1	24.8	14.4	0.92	0.5 - 1.4	0.74
GFD is expensive	50.4	10.4	29.9	9.3	1.74	0.9 – 3.0	0.05
I don't understand what I can eat	5.1	55.7	6.7	32.5	0.77	0.3 - 1.6	0.50
I don't understand food labelling	2.1	58.7	6.7	32.5	0.22	0.9 - .56	**<0.01**
Dietitian gave me information pack	57.3	3.5	37.6	1.6	1.04	0.2 – 3.6	0.94
Contact telephone given by dietitian	48.3	12.5	34.9	4.3	0.37	0.1 – 0.8	**0.02**

OR: Odds ratio, CI: Confidence Interval

Factors achieving significance were: membership of the CS (p<0.01), understanding what to eat (p=0.05), affordability of GFP (p=0.05), contact information given to the patient (p=0.02) and understanding food labelling (p<0.01) (Appendix 4.1J)

GFD adherence as assessed by CDAT questionnaire

CDAT scores from all 375 participants were calculated from the cumulative scores of individual components; based on that, patients were divided into two groups namely: adherent to GFD (CDAT <13) and non-adherent to GFD (CDAT>13). CDAT scores for the entire population (n=375) ranged from 7 to 30 (Med= 13, IQR= 10-19) and were not distributed normally ($p<0.01$), with skewness of .65 (SE = .21) and kurtosis of -.32 (SE = .25). There was no significant relationship of increasing score with gender and ethnicity (Appendix 4.1Kc&d).

The most prevalent score was 9 (n=35), followed by 12 and 7 (n=32). Wilcoxon Signed rank test showed that there was a significant relationship between CDAT score and increasing age; (n=375), $z=-16.6$, $p<0.01$, $r= -.8$ (Appendix 4.1Ke). Individual scores against the number of patients are presented in the clustered bar chart below (Figure No 20).

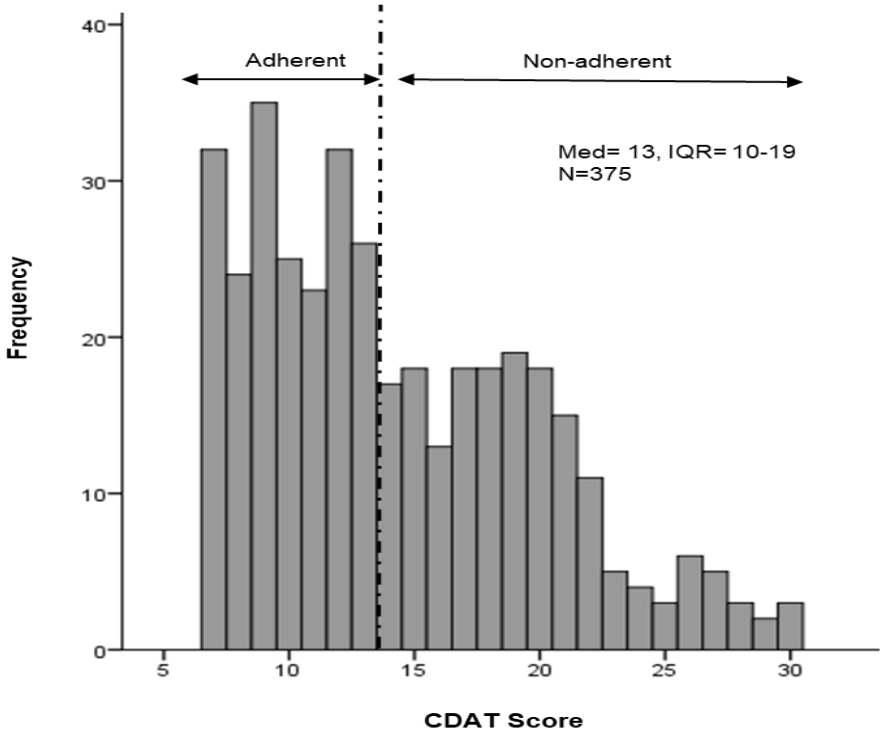

Table 20 : CDAT score of the population (n=375). Line shows the cut-off point of the adherent (to the left CDAT score <13) and the non-adherent groups. IQR=Interquartile range.

Males and females had similar CDAT scores (Mdn=13, n = 108 and Mdn=13, = 267 respectively); MWU, U = 14293.5, z = -.131, p = .896, r=-.00. Similarly, there was no relationship between ethnicity and increasing CDAT score (Appendix 4.1Kc&d). The adherent and non-adherent groups are further compared according to CDAT scores in the table below (Table No 21).

Table 21: Comparison of adherent and non-adherent patients based on CDAT score.

		CDAT Score		
Variables	**Total**	**CDAT <13**	**CDAT >13**	***P* Value**
	375	n=171 (45.6%)	n=204 (54.4%)	
Median Age (IQR)	50 (33-60)	53 (33-63)	47 (32-58)	**0.04***
Age Groups				0.08**
< 20 years	24 (6.4%)	10 (5.8%)	14 (6.9%)	
21-30 years	59 (15.7%)	26 (15.2%)	33 (16.2%)	
30-40 years	42 (11.2%)	14 (8.2%)	29 (13.7%)	
41-50 years	69 (18.4%)	27 (15.8%)	42 (2.6%)	
51-60 years	91 (24.3%)	43 (25.1%)	48 (23.5%)	
61-70 years	48 (12.8%)	31 (18.1%)	17 (8.3%)	
> 70 years	42 (11.2%)	20 (117%)	22(10.8%)	
Gender				0.45**
Male	108 (28.8%)	46 (27%)	62 (30.4%)	
Female	267 (71.2%)	125 (73%)	142 (69.6%)	
Ethnicity				0.25**
White Caucasians	337 (89.9%)	157 (92%)	180 (88%)	
South Asians	38 (10.1%)	14 (8%)	24 (12%)	
Sikh	20 (5.3%)	6 (3.5%)	14 (6.9%)	
Muslim	9 (2.4%)	4 (2.3%)	5 (2.5%)	
Hindu	9 (2.4%)	4 (2.3%)	5 (2.5%)	

***WRS test **Chi Square test, IQR= Interquartile range**

It is evident from the table above that gender and ethnicity are not significantly associated with adherence based on CDAT score dichotomised at CDAT score of 13, whereas age is associated with better adherence; CDAT<13 (Mdn=53, n = 171) and CDAT>13 (Mdn=47 , n=204), U = 15328, z = -2.02, p = .04, r=-.10 (Appendix 4.1Lc-e).

Several factors were analysed between adherent (CDAT<13) and non-adherent (CDAT<13) groups and among them “Do you get GF food on prescription”, “I don’t understand what to eat”, “I don’t understand food labelling”, “GF diet is unpleasant” and “Membership of Coeliac UK” were significantly associated with CDAT score of less than 13. The results are displayed in the Table below (Table No 22) (Appendices 4.1Ma-h)

Table 22: Factors associated with low CDAT scores.

Variables	CDAT <13 (n=204)		CDAT >13 (n=171)				
	Yes	No	Yes	No	χ2	Phi	P* Value
Do you get GF food on prescription	139 (81%)	32 (19%)	139 (32%)	65 (68%)	8.8	.15	<0.01
I don’t understand what to eat	157 (92%)	14 (8%)	174 (85%)	30 (15%)	3.81	-.10	0.05
I don’t have time to prepare a meal	162 (95%)	9 (5%)	187 (92%)	17 (8%)	1.35	-.06	0.24
My GP does not prescribe enough GFP	165 (96%)	6 (4%)	177 (87%)	27 (13%)	.71	-.04	0.39
I don’t understand food labelling	165 (96%)	6 (4%)	177 (87%)	27 (13%)	10.96	-.17	<0.01
GF diet is expensive	136 (80%)	35 (20%)	165 (81%)	39 (19%)	.10	-.01	0.74
GF diet is unpleasant	90 (53%)	81 (47%)	133 (65%)	71 (35%)	6.09	-.12	0.01
Membership of Coeliac UK	89 (52%)	82 (48%)	126 (62%)	78 (38%)	7.18	.13	<0.01

***Chi Square test**

It may be noted that these results are in agreement with the results generated from the binary logistic regression for the Butterworth questionnaire (Table No 19, page 93) in relation to membership of Coeliac UK and “I don’t understand food labelling.”

CDAT score was a combination of several statements categorised as: symptoms, social, psychological and gluten exposure. The most prevalent answer was low energy (70%), followed by reports of difficulties while dining out (69%). Similarly the mean score for low energy was the highest (1.9) followed by difficulties dining out. The mean score for those who ate gluten on purpose was 0.1 and this was the lowest. The results of median scores of individual components of CDAT are shown in the Table below (Table No 23).

Table 23: Comparing CDAT sub score of the responders (n=375) based on gender and ethnicity.

		Gender			Ethnicity		
	Total	Male	Female		White	Asians	
	375	108 (32.2%)	267 (67.8%)		337 (89.9%)	38 (10.1%)	
Statements in CDAT Score	Mdn (IQR)	Mdn (IQR)	Mdn (IQR)	***p***	Mdn (IQR)	Mdn (IQR)	***P****
Symptoms of CD							
Low energy?	2 (1-3)	2 (1-3)	2 (1-4)	**0.02**	2 (1-3)	2 (1-3)	0.91
Headache	2 (1-3)	1 (1-3)	2 (1-3)	**0.01**	2 (1-3)	2 (1-3)	0.75
Social Issue							
Follow GFD while dining out?	2 (1-4)	2 (1-4)	2 (1-3)	0.32	2 (1-4)	2 (1-4)	0.80
Psychological							
Consider the consequences	2 (1-2)	2 (1-3)	2 (1-2)	0.30	2 (1-2)	2 (1-2)	0.16
Don't consider myself a failure	1 (1-2)	1 (1-3)	1 (1-2)	0.53	1 (1-2)	1 (1-3)	0.41
Gluten Exposure							
Accidental gluten exposure?	1 (1-3)	2 (1-3)	1 (1-3)	0.34	1 (1-2)	2 (1-4)	**0.00**
Eaten gluten on purpose?	1 (1-2)	1 (1-2)	1 (1-2)	0.72	1 (1-2)	1 (1-2)	0.77
Overall CDAT score	13 (10-19)	13 (9-19)	13 (10-18)	0.89	13 (10-18)	13 (10-19)	0.28

***MWU test, IQR= Interquartile range, Mdn= Median value**

It is evident in the table above that there is no difference in total CDAT score based on ethnicity and gender, but sub-group females were significantly more symptomatic as compared to males. Further analysis of the individual statements showed SA reported significantly more accidental ingestion as compared to White Caucasians (Appendix 4.1N a & b).

The individual domains (symptomatic, social, psychological and gluten exposure) were compared and the non-adherent group had universally increased mean scores. This is displayed in the Table below (Table No 24) (Appendix 1.4O)

Table 24: Comparison of adherent and non-adherent patients based on CDAT score.

Variables	N (Total)	CDAT Score		*P* Value*
		CDAT <13	CDAT >13	
	375	171 (45.6%)	204 (54.4%)	
	Median (IQR)	Median (IQR)	Median (IQR)	
Symptoms of CD				
Low energy?	2 (1-3)	2 (1-2)	3 (2-4)	**0.00**
Headache	2 (1-3)	1 (1-2)	3 (2-4)	**0.00**
Social Issue				
Follow GFD while dining out?	2 (1-4)	1 (1-2)	3 (2-4)	**0.00**
Psychological				
Consider the consequences	2 (1-2)	1 (1-2)	2 (1-3)	**0.00**
Don't consider myself a failure	1 (1-2)	1 (1-1)	2 (1-3)	**0.00**
Gluten Exposure				
Accidental gluten exposures?	1 (1-3)	1 (1-1)	2 (1-3)	**0.00**
Eaten gluten on purpose?	1 (1-2)	1 (1-1)	2 (1-3)	**0.00**
Overall CDAT score	13 (10-19)	9 (8-11)	18 (15-21)	**0.00**

*MWU test, IQR= Interquartile range, Mdn= Median value

Comparing adherence based on the CDAT and Butterworth criteria

The questionnaires described above use different criteria to categorise a patient as adherent or non-adherent. Butterworth and colleagues (2004) for example use ingestion of gluten (any amount), whereas Leffler and colleagues (2009) use CDAT score of >13 as non-adherent to a GFD. Although the Leffler questionnaire also has one statement about ingestion of gluten, it relies on several other categories in addition to that. The two questionnaires will now be compared, to evaluate their sensitivity for detecting non adherent patients. Using the strict Butterworth criterion, 147 (39.2%) were non-adherent; in contrast, using the Leffler criterion, 204 (54%) were non-adherent out of 375 responders. This means that the Leffler questionnaire detected an extra 57 (14.8%) patients who were non-adherent to a GFD. When this was further compared it was evident that 11 patients who were non-adherent according to Butterworth were adherent according to Leffler. Similarly, 68 patients who were adherent according to Butterworth were non-adherent according to Leffler. This is presented in the comparative graph below (Fig No 10)

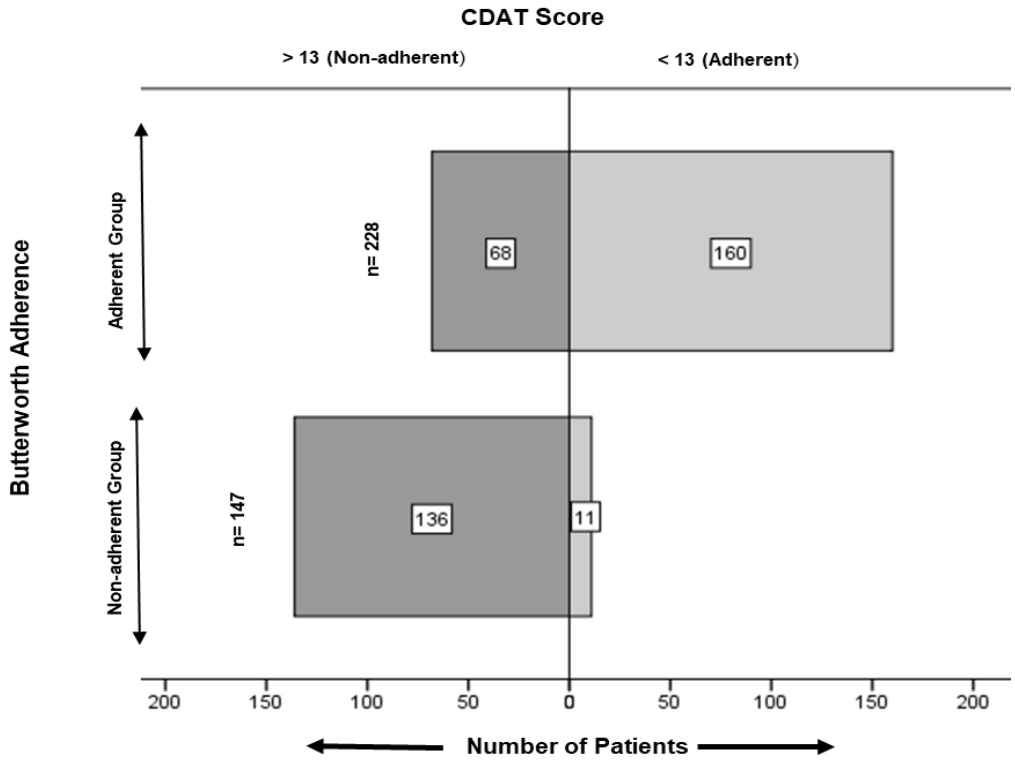

Figure 10: Comparing Butterworth and Leffler adherence questionnaires.

Next the sensitivity and specificity of the Butterworth questionnaire were calculated and are shown in the Table below (Table No 25).

Table 25: Diagnostic accuracy of the Butterworth questionnaire

	Value	95% CI
Parameters		
Sensitivity	93.96%	89.44% to 96.94%
Specificity	75%	69.41% to 80.03%
Positive Likelihood Ratio	3.76	3.05 to 4.63
Negative Likelihood Ratio	0.08	0.05 to 0.14
Positive predictive value	71.55%	67.11% to 75.61%
Negative predictive value	94.88%	91.24% to 97.06%
Accuracy	82.6%	78.79% to 85.97%

This shows that the Butterworth questionnaire is 6% less sensitive than the Leffler questionnaire for the purpose of detecting adherence rates in a given population. The sub-categories of the Butterworth method were further analysed according to Leffler adherence. The whisker chart below shows that all those who were non-adherent in the moderate (20.8%) and severe (4.5%) categories on the Butterworth criteria, were also non-adherent on Leffler score. The mild category had 84 (47.2%) patients and 8.6% (n=17) were adherent on the Leffler method. This is evident from the wide range of Leffler scores in this category on the whisker chart below (Figure No 11)

The

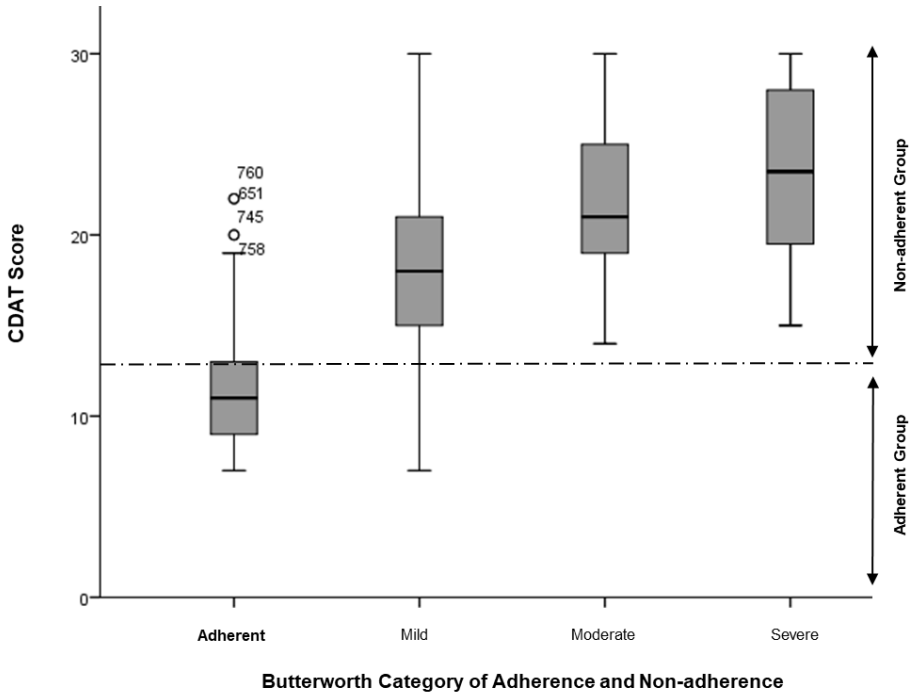

Figure 11: Comparing individual Butterworth categories and CDAT score

whisker chart above shows that the average total Leffler score increases as the severity of the non-adherence increases. Furthermore, in the moderate and severe non-adherence groups, the Butterworth questionnaire has comparable sensitivity to the Leffler questionnaire, as all those who are non-adherent in the latter are non-adherent in the former; but in the mild group the data is not consistent between the questionnaires.

Themes from participants' comments

Additional comments were received from 63 patients (16.8%), ranging from short phrases to descriptions related to different sections; they fell into five themes. The predominant theme was related to inadvertent ingestion of gluten by 48 patients in different settings including: dining out in restaurants (n=40) or friends' houses (n=20), or even accidentally buying GCP (n=6). Patients' comments in relation to a GFD included:

"Sometimes you find out late, too late, someone has fed you with a gluten containing stuff", "Rarely, though, I may take gluten without any intention", "…by mistake I do take gluten now and then" and "accidental ingestion, very rare though."

The second most common theme was change of address (n=11) or contact details (n=3), followed by the third most common theme: weight gain on a GFD (n=7).

"Hate it!!! I have gained weight on gluten free stuff", "I was so slim, on gluten free diet I have gained weight", "well weight gain is a new issue with this gluten free diet" and "slight weight gain while on gluten free diet."

The fourth most common theme was related to the difficulty in obtaining GFF from Asian shops and takeaways, as the owners lacked awareness of GFP (n=6).

"No gluten free diet in local stores", "Sorry but cannot get gluten free diet from local stores, not sure if they even know what gluten free means!!" and " Asian stores have no gluten free food items"

The final category contained miscellaneous/unclassifiable comments (n=5) such as: difficulty following a GFD during a period of depression, redundancy related to CD symptoms, inability to find a priority toilet for diarrhoea related to CD and issues with the hospital menu during admission.

Clinical correlation

Clinical letters and computerised record analysis

All 375 patients gave permission for their health records to be accessed. IDA was present at some stage in 216 (57.5%) patients. Autoimmune diseases were the next most commonly associated conditions, affecting 50 patients (13.3%), followed by depression which affected 47 patients (12%). The relative frequencies are displayed in the car chart below (Fig No 12)

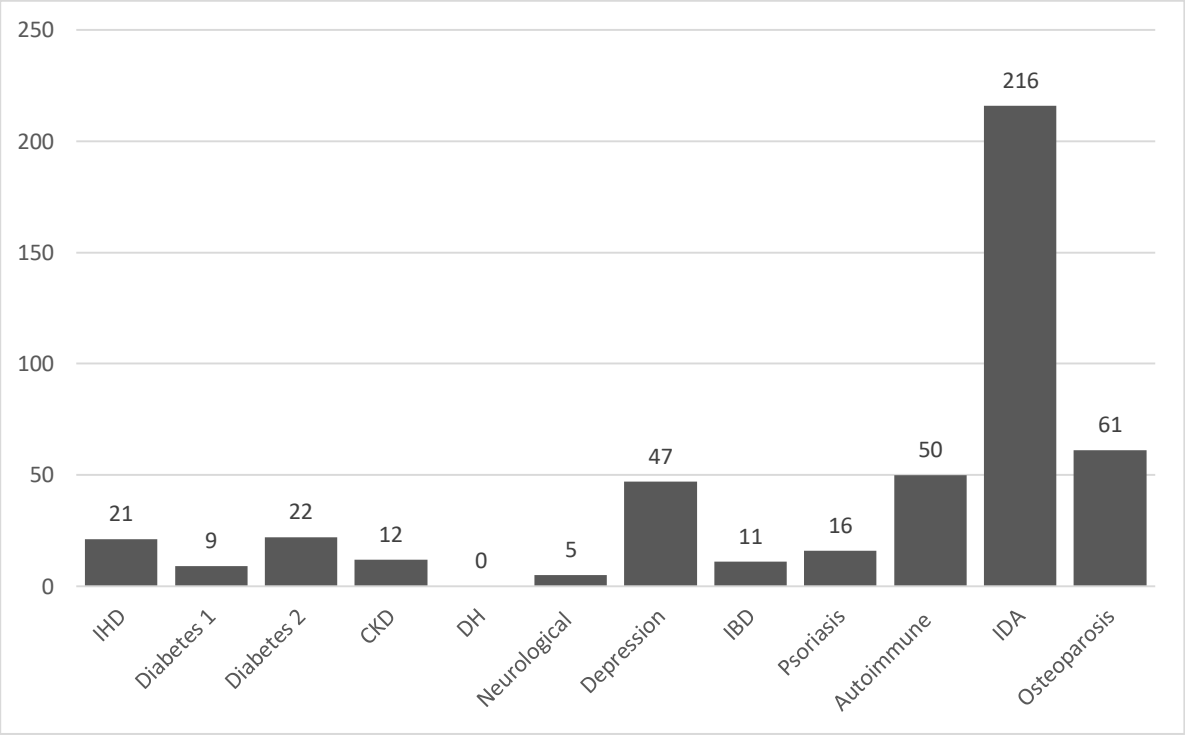

Figure 12: Disease frequency among CD patients. IDA=Iron deficiency anaemia, DH=dermatitis herpetiformis, CKD=Chronic kidney disease, IBD= iInflammatory bowel disease, IHD= Ischaemic heart disease.

The diagnosis of depression was made on the basis of an assessment by a qualified psychiatrist; being on anti-depressants prescribed by the GP was not considered adequate for diagnosis. Frequencies of common health conditions are shown in the bar chart above. Since these records were extracted from patients' clinical data and none of these tests was done as part of this study, only those parameters for which a full record was available were selected. The clinical conditions were compared for significance ($\chi 2$ test) in relation to adherence to a GFD, as determined by CDAT scores, and no significance difference was found, as shown in the Table below (Table No 26) (Appendix 4.1P)

Table 26: Conditions in relation to GFD adherence as measured by CDAT in CD patients.

Blood Parameter raised	No of Patients	χ2	Phi	*P* Value
Ischaemic heart disease	10	.00	-.001	.989
Diabetes Type 1	5	.24	-.025	.623
Diabetes Type 2	11	.06	-.013	.80
Chronic Kidney Disease	4	.99	.051	.319
Depression	24	.27	-.027	.597
Inflammatory Bowel	5	.018	.007	.89
Osteoporosis	25	1.239	.057	.538
Autoimmune diseases	23	.050	.012	.823

Haematological and biochemical parameters

Analysis of laboratory values showed that certain haematological parameters were found to be raised. Among these, the liver function test Alanine Transferase (ALT) was raised in 10 patients (2.7%), Alkaline Phosphatase was raised in 20 patients (5.3%), whereas Bilirubin was raised in 24 (6.4%) patients. The Table below (Table No 27) shows the frequency of elevated blood test results amongst the patients (Appendix 41.Q)

Table 27: Laboratory values in relation to CD patients (n=375).

Blood Parameter raised	No of Patients	Percentage
Alanine Transaminases (ALT)	10	2.7
Bilirubin	24	6.4
Alkaline Phosphatase	20	5.3
White cell count (WCC)	9	2.4
Mean Corpuscular Volume (MCV)	6	1.6
C reactive proteins	34	9.1
Platelets	59	15.7

Next the clinical conditions were compared for significance (χ2 test) in relation to GFD adherence of the patients: no significant difference was found, as shown in the Table below (Table No 28).

Table 28: Laboratory values in relation to CD patients.

Blood Parameter	No of Patients	χ2	Phi	*P* Value
Bilirubin	7	3.44	.096	.063
Phosphate	6	1.36	-.060	.243
Calcium	17	1.107	-.054	.293
Magnesium	14	1.326	.059	.515
White Cell Count	3	1.446	.062	.485
MCV	120	1.232	.057	.540
Neutrophil	8	1.336	.060	.513
CRP	17	.096	-.016	.756
Iron Deficiency	106	.528	-.038	.468

CRP= C reactive protein

SECTION III

Discussion

The “No Triticeae” study explored the demographics of CD in a Leicestershire population and specifically attempted to determine the adherence rate to a GFD by two different instruments, namely the questionnaires by Leffler and colleagues (2009) and Butterworth and colleagues (2004). Additionally, the study looked into the causes of non-adherence to a GFD and views on CD from patients’ perspectives, involving both Caucasians and SA patients. The study was a follow up to the MSc project by the author (Muhammad, 2013), with significantly larger power and additional collected data. In relation to the Index study by Butterworth et al., (2004) which used the same questionnaire, it was evident that the adherence to a GFD in this study (60.8%) was not significantly different from Butterworth’s finding (62%). There were, nonetheless, differences in the power, as we finally received 375 completed questionnaires as compared to 87 questionnaires in Butterworth’s study (2004).

Choice of methodology

The study used a postal questionnaire survey to assess adherence to a GFD and aspects of quality of life in patients diagnosed with CD who were theoretically on a GFD. Such a study design offers several advantages such as: data related to all variables is collected simultaneously, it is time efficient, it offers analysis of multiple outcomes and exposures and may aid in measurement of prevalence. Moreover, there is no risk of “loss to follow-up” with such a methodology. The main drawbacks of such an approach, however, include: its dependence on RR, difficulty in making causal inferences and susceptibility to recall bias (Bland, 2015). Two questionnaires, using the postal service, were used to gather data in this study. Questionnaires are routinely used in social research (Brace, 2008) and it is a special kind of conversation where patients are engaged to collect information; it is also a common tool used by physicians (Kumar & Phrommathed, 2005) for this purpose. The method itself demands structured methodology (Richardson, 2004) and ethical considerations (Evans et al., 2002) and these issues were addressed while conducting this study. Both of the questionnaires had been used in previous studies (Butterworth et al., 2004, Leffler et al., 2009) and the questionnaire by Leffler et al., (2009) had also been validated previously. Similarly, questionnaires have been used in CD research in relation to adherence to a GFD in many studies (Biagi et al., 2009, Butterworth et al., 2004, Rosen et al., 2011, Pietzak, 2005, Sainsbury et al., 2013b, Villafuerte-Galvez et al., 2015, Rajpoot et al., 2015) with slightly

different designs and questionnaire contents. Furthermore, such a mode of delivery was considered economical when analysed in comparison with other modes of delivery in a study (Sinclair et al., 2012). An on-line questionnaire was another available option, but access to individual email addresses was not available and, more importantly, the computer literacy of the population approached has not been studied, hence we decided against it. Additionally, a previous Leicestershire based study (n=466) did not find any significant difference in the non-response rate between online and paper based questionnaires (Denscombe, 2009), although it is accepted that the study population was different from that in our study. It is therefore felt that this study derived maximum advantage using the postal questionnaire approach, in terms of accessing a widely scattered population.

Diagnoses of CD per year

It is evident from this study that the number of patients diagnosed per year (from 2004 to 2014) increased over time. This may reflect an increasing trend of CD diagnosis at UHL. However, this must be interpreted with caution, as this apparent rise in the number of diagnoses of CD per year does not equate to the true incidence of CD, as it was not calculated for the whole population of Leicestershire (because of un-availability of data and not being an aim of this study). This finding, however, gives an indirect impression that there is an increasing incidence (hence prevalence) of CD in the Leicestershire area, which follows the previously defined trend of increasing epidemiological parameters for CD worldwide (Rewers, 2005, Murray et al., 2003b, Altobelli et al., 2014, Riddle et al., 2012, Rubio-Tapia et al., 2009, Lohi et al., 2007). Several reasons for this increased incidence have been cited in the literature, such as increased availability of sensitive serological tests and increased awareness among physicians to use these tests (Ludvigsson et al., 2013a), yet an environmental factor cannot be excluded (Riddle et al., 2012, Welander et al., 2010, Stene et al., 2006).

The rate of diagnosis of CD at UHL will vary, depending on multiple factors. Firstly, not all patients had the diagnostic indication for D2 biopsies, as a proportion of them would have been diagnosed before 2004 (the starting year of data collection) and will be having follow up biopsies. Secondly, the diagnosis of CD in a given population per year is dependent on the number of endoscopies performed in that period. This means that a falsely high number of CD cases may be diagnosed, if more endoscopies were performed in that particular year. Thirdly, pathologist related factors such as staff sickness and mandatory leave may also affect the numbers of slides reviewed per year in order to diagnose CD.

Fourthly, the number of referrals made by General Practitioners (GP's) per year will also affect the figures.

It is thus suggested that these figures must be audited prospectively by taking into consideration all the factors to arrive at correct figures. This may be achieved by first collecting all available data and then analysing it to ascertain the cause; future projection of the number of patients with CD should be determined, so that healthcare budget allocation can be assigned judiciously.

Study population and return rate

The study population was all inclusive except for the paediatric age group (which was outside the scope of this research) and those who had learning difficulties. The SNOMED® database at UHL has information on over 2000 patients, but we only selected patients diagnosed between 2004 and 2014. Based on the MSc pilot study (Muhammad et al., 2013) and published data, this power (n=972) was considered sufficient to meet the study aims. The number of CD patients evaluated with questionnaires in other studies has been diverse depending on the research question (Leffler et al., 2007, Chauhan et al., 2010). Our index study reported data from 130 adults with CD (Butterworth et al., 2004).

The combination of histological diagnosis of CD coupled with positive serology was chosen for increased sensitivity and specificity (Donaldson et al., 2008). This method has the disadvantage of missing that small number of patients who never had biopsy to diagnose CD, as they either had a contraindication for an endoscopic procedure or biopsy, or their diagnosis was established on clinical grounds coupled with serology (which has sensitivity and specificity of over 95% (Hill, 2005)). In addition to that, patients who were diagnosed with capsule endoscopy, which is an alternative (Rondonotti et al., 2007), although less sensitive (Rokkas & Niv, 2012) way of diagnosing CD, may also have been missed. The study thus approached the diagnosis from a very objective standpoint and in a way that provided the power needed to reach meaningful conclusions.

Gender distribution of the sample and female predominance

There was a female predominance in our study population, which reflected the previous trend of CD presentation in the general population (Murray et al., 2003a, Green et al., 2001). The ratio of female to male was 2:1 in this study and this figure is close to that in previous published research (Megiorni et al., 2008). A recent US based study (n=982) reported an even higher ratio of 5.5:1 (Joelson et al., 2018a),

but the diagnostic criteria in this study did not base the diagnosis entirely on duodenal biopsies. Historically, several studies have reported the ratio and it depends on the sample size and methodology, although it is accepted that all have reported female predominance in the samples and the cause for this finding remains obscure.

Green et al (2001) reported a higher ratio of 2.9:1 for females based on a large sample (n=1,612) where 75% had biopsy proven CD. However, the sample in this study came from a coeliac advocacy group which had a female predominance to begin with. Furthermore, the higher rate may well represent response bias, where females might have responded to the questionnaire more than males (Smith, 2008, Rübsamen et al., 2017), thus leading to a higher ratio than our sample. Similarly Murray (2003b) analysed data between 1950 and 2001 in a US based study and reported a ratio of 2.4:1, which is close to our study and the strength of Murray's study lies in its access to detailed data from the Rochester Epidemiology Project (REP, 2018) spanning over 50 years. Collin and colleagues (1994) reported a lower ratio of 0.34:1, but the sample selected came from symptomatic patients and there is a possibility that it had selection bias. There is therefore variability in the reports of female predominance in samples.

Our study therefore follows the trend of the previous reports of increased numbers of females being diagnosed, but since studies done to ascertain the ratio between males and females are diverse in terms of methodology, sample selection, period of diagnosis and availability of diagnostic criteria, it is difficult to know if our study is reporting the true ratio. Despite these methodological differences, the question of whether this discrepancy in gender ratio is real is difficult to ascertain. There is also a suggestion that such a ratio disappears with advancing age (Fasano et al., 2003), although this study only used screening methods in the population in contrast to other holistic methodologies such as patients' records, histological data and questionnaires.

One may argue that there are gender differences in health related help-seeking behaviour (Oliver et al., 2005) and there is evidence to suggest that females attend their GP more often (Vedsted & Christensen, 2005, Corney, 1990) than their male counterparts (Galdas et al., 2005) and this might have led to more female cases being identified, but the evidence presented in support of this argument is weak and based on low powered and possibly biased studies. Another possible explanation might well be the exclusive female consultations in relation to fertility, obstetric and gynaecological issues, which have a clear association with CD (Stazi & Mantovani, 2000). Linked to this concept is anaemia which again is a presenting sign of CD (Harper et al., 2007), is common in pregnancy (Goonewardene et al., 2012) and

necessitates CD testing, thus skewing the diagnosed case burden in favour of one gender. Osteoporosis is another condition which is associated with CD (McFarlane et al., 1995) and is more common in the female gender (O'neill et al., 1996); this may also increase the number of females in the sample. It is thus concluded that our sample is close to a representative ratio of 2:1.

Response rate of the questionnaire

The RR for this study was 38.6%, whereas the reported average RR with a questionnaire is 52% (Baruch & Holtom, 2008); RR will vary depending upon the target audience and distribution method (Ekhtiari et al., 2017). The variability in absolute RR ranges from 14% to 91% as assessed by a study (Cummings et al., 2001) and this is multifactorial (Richards, 2007, Edwards et al., 2009).

Although it is not clear what is a minimally acceptable rate (Richardson, 2005), it has been suggested that rates above 80% are generally good, but rates between 40-80% are acceptable, as suggested by Gehlbach (Gehlbach, 1993). Similarly, Cummings and colleagues (2001) analysed studies looking into the RR to physician postal questionnaires spanning more than four decades. They inferred that, with passage of time, the RR has increased gradually and has reached a plateau. They concluded that, on average, RR was generally 62% for small to medium studies, but 52% for larger studies. Similarly, our index study (Butterworth et al., 2004), which used the same questionnaire, had a RR of 66.9%. Our MSc pilot project, using the same but contracted cohort, had a RR of 57.8% and, looking at the RR of this study, one can argue that it is close to the lower range of acceptability.

The survey was mailed and took on board suggestions by Edwards and colleagues (2009) to increase the RR, however a decrease in the survey response was noted as compared to the MSc project (Muhammad et al., 2013). This may be explained by the length of the questionnaire, as this study in comparison to the MSc project was 60% longer. This question was examined by a study which concluded that longer questionnaires (more than seven pages) had RR closer to 40.5% (Iglesias & Torgerson, 2000) and this description matches our study in terms of length of questionnaire and the related RR of 38.5%.

In addition to that, the MSc project (Muhammad, 2013) questionnaire could be finished in one sitting by patients, whereas this survey required the participants to provide a prospective diary of food intake for three consecutive days. This factor is important, as the diary RR was 15% in comparison to the

questionnaire RR of 38.6%. It is thus inferred that length of questionnaire affects the RR as previously shown (Kalantar & Talley, 1999, Galesic & Bosnjak, 2009, Dillman et al., 1993).

This study reports a low RR for patients of SA ethnicity and this finding was significant. This is in contrast to published literature about ethnicity affecting RR, as one systematic review did not find any difference (Sykes et al., 2010) in the RR for all non-white minorities and the results of this may not be generalised to SA communities in the UK. Sheldon and colleagues (2007) on the other hand found that RR was low for black and ethnic minorities, but this was in a report to NHS authorities and was poorly referenced. Similarly a Danish study reported the RR in such a population to be low (24%) in a recent study (Bodewes & Kunst, 2016). A UK based study (n=9,100), involving SA, reported a recruitment rate of 8% in a questionnaire based study (Malavige et al., 2015) which is very low. However the results need to be interpreted with caution, as the survey was related to sexual health and this is considered a social taboo, naturally leading to a reduced response. Previous observation by Professor John F Mayberry (personal communication) has shown that Asian populations tend to have lower RR, for which possible explanations were cultural or literacy related. Additionally, the sensitive nature of the questionnaire may reduce RR in SA. Importantly, this issue is significant from the point of view of future CD related research among minority communities which have the same CD prevalence as White Caucasians. High-powered interview based research involving only Asian patients should be organised to explore the causes behind poor RR.

On the contrary, there was no significant difference in returners and non-returners when analysed according to gender. This area has been examined previously and conflicting results have emerged; there is weak evidence to suggest that females respond better than males (Smith, 2008). In our index study and other research into CD related questionnaires this effect was not observed and there was no difference between the RR of different genders (Butterworth et al., 2004, Leffler et al., 2009). It may be argued that the study by Smith (2008) was targeting a selective group of university faculty students and clinical studies like ours have a different set of patients, so the apparent departure of Smith (2008) may be explained by selection bias.

Our study reports that increasing age is significantly related to poor RR. This area too has conflicting results and one study, for example, has reported that younger age has been noticed to affect the survey response positively (Kaplowitz et al., 2004), but the methodology involved the internet as well as postal routes. In addition to that, the study recruited university students with age ranges between 24 and 30

years and 80% of them were 24 years or younger, suggesting sample bias; the study itself does not claim to have reached the conclusion. Similarly another recent well organised study from the US Army found that RR was low in younger personnel (Miller & Aharoni, 2015), but again this study had a contracted age range. In addition to that, an earlier but comprehensive systematic review did not find any evidence of age or gender affecting survey RR, agreeing with our findings (Asch et al., 1997).

Health problems in childhood and age at diagnosis

Our study reports health related problems in childhood in around 30% of the patients. This area is difficult to present as objective evidence, as it is affected by recall bias, although it is accepted that a significant number of patients are undiagnosed in childhood (Bingley et al., 2004, Cosnes et al., 2002). Other studies in this area have relied on serological diagnosis hence cannot be compared with our findings. It is suggested that true figures may only be possible by prospective studies and may be objectively researched by exploring childhood health records rather than relying on recall based data. Age at diagnosis in our study shows two peaks: firstly between the ages of 18 and 30 and then between 51 and 60 years of age; this late peak was reported in previous research (Vilppula et al., 2011, Vilppula et al., 2009).

Symptoms of CD

Fatigue was the most common symptom in those who responded to the questionnaire. It is interesting to note that fatigue has gradually taken over from the symptom of diarrhoea in the past decade or so (Feldman et al., 2015). Fatigue is commonly found as the presenting feature in CD, as suggested by a study which explored the role of fatigue in 71 untreated CD patients (Siniscalchi et al., 2005a) and our results follow this trend. Of interest is the generalised nature of fatigue and its relationship with depression (which again is related to CD) and it is thus possible that some in our cohort had associated depression leading to fatigue (Chaudhuri & Behan, 2004). It has been suggested that in future studies the Depression Anxiety Stress Scales (DASS) should also be measured when evaluating CD and its symptomatology (Crawford & Henry, 2003). Similarly, it was noted that 51% of our patients reported diarrhoea alone or in combination with other symptoms. This is in accordance with previous reports that half of the patients present with chronic diarrhoea (Green & Cellier, 2007).

66% of our patients presented with symptoms suggestive of vague abdominal pain and bloating and this has been reported to range from 46% to 70% (Corazza et al., 1996, van der Wouden et al., 2007, Zipser

et al., 2003). Additionally, these are also principle symptoms of IBS (Drossman et al., 2009), a functional disorder of the GI tract, which overlaps in symptomatology with CD (Ford et al., 2009). Our study thus follows the previously reported trend. Comparing the effect of gender on presentation, our study reports that symptoms of fatigue and nausea were significantly more common in females than in males. Previous research had suggested that there were no gender differences in the mode of presentation of CD (Bai et al., 2005), although the authors accepted that males tended to have greater malabsorption. Although we report this for the first time, our report needs further verification by in-depth interview for a more holistic picture.

Comparing the symptomatology on ethnic grounds, it is clear that Asians tend to report more stomach pain and vomiting. Previous research using a similar cohort reported that SA with CD are less likely to present with 'irritable bowel syndrome' symptoms, but more likely to have features of vitamin D deficiency, iron deficiency and have a higher alkaline phosphatase than White Caucasians (Butterworth et al., 2005). Although we did not analyse the results in terms of irritable bowel syndrome, abdominal pain and vomiting may be partly related to irritable bowel syndrome (Sanders et al., 2003), thus, reporting contrary results to this study. Our study (n=38) is comparable in power to the study by Butterworth and colleagues (2005) where there were 40 patients, but the methodology is different, as our study used questionnaire based data and their study used retrospective clinical notes based data; both approaches have their pros and cons. It is thus suggested that an audit should be designed which examines this issue more holistically e.g. a prospective study, in newly recruited patients over a number of years, within the outpatient department, in the form of a history taking audit.

The symptomatology of CD is changing and thus this issue needs exploration, as GPs need to be aware of the emerging symptomatology of CD and not looking for classical symptoms before testing for it. Research in this area will hopefully increase case detection as previously suggested (Sanders et al., 2003), as it is low in the general population (Kolho et al., 1998). Additionally, based on the presenting symptoms and classification of CD, the most prevalent group was non-classical CD and this is the group which has dominated the clinical picture of CD in reported studies (Dewar & Ciclitira, 2005, van Heel & West, 2006, M. Bardella et al., 2007). Finally, when clinical presentations were analysed according to gender of the patients, there was no significant difference between males and females and this is in accordance with previously reported research (Nachman et al., 2009).

Diagnostic delay in CD

In relation to the first presentation of symptoms and the final histological diagnosis, the average gap in this study was 6 to 12 months. Delay in diagnosis is a recognised phenomenon and, although it is multifactorial, it is argued that it is the clinician who fails to recognise the disease, rather than the patient failing to seek medical care, as suggested by Green and Jabri (2003) in a review. Other authors have suggested that a delay in diagnosis has a negative effect on HRQoL (Norström et al., 2011) and on cancer in CD (Silano et al., 2007). The time interval in our study, in comparison to previous research, is contracted (Corazza et al., 1996, Green et al., 2001).

Although there is no robust data examining the delay in diagnosis, this discrepancy may well be explained by the methodology of our study. A previous Canadian study (n= 5,240) has reported a mean delay of 11 years (Cranney et al., 2007). Similarly, a questionnaire based study (n=2,000) from the UK, similar in return rate to our study (40%), reports the delay to be 13 years (Gray & Papanicolas, 2010).

The possibility of such a swift diagnosis in this centre is explained by many factors, but important among them is the way the survey question was posed i.e. “How long had you been experiencing symptoms before you were diagnosed?” The question was followed by a choice of four answers and also unified two concepts (the symptoms and diagnosis) which may mean different things to different patients. It is possible, for example, that patients may infer from the word diagnosis: “first explanation by the GP”, “referral to the hospital consultant and his explanation”, “blood test and results” or “endoscopy and biopsy results”. All these concepts are on a time line and, depending upon the interpretation of the survey question, may be answered differently by different patients depending on their understanding. This phenomenon has been discussed by well-established authors in this field (Schuman & Presser, 1996) and has implications for our study.

Another reason which may explain this phenomenon is recall bias (Coughlin, 1990), as patients tend to recall things close to important events, which in this case was the diagnosis of CD and perhaps symptomatic improvement with a GFD. Additionally, our cohort was based on histological diagnosis, whereas other surveys had different methodologies such as postal invitations to members of the CS (Gray & Papanicolas, 2010) or the Canadian Celiac Association (Cranney et al., 2007), where the sample clearly has high power (n=2,000 and 5,240 respectively). The sample which is identical in demographic characteristics to the index study (Butterworth et al., 2004) reports this delay to be 9.4

and 5.3 years for Caucasians and Asians respectively; these figures were obtained either from clinical notes or interview, as the questionnaire does not have the ability to measure this value with such accuracy. A limitation of our study was the question technique and it is suggested that future survey should have open ended question without giving multiple choice options and preferably with the addition of another question about the date of gastroscopy and biopsy sample.

Consultation with physician and dietitian

Our study reports high satisfaction rates (> 90%) with both physician and dietitian and this suggests almost equal involvement of physician and dietitian in the management of CD. This is in accordance with Bebb et al., (2006), who examined a cohort of 126 CD patients (80% adherent to a GFD) and they were asked about different options in FU i.e. clinician, dietitian, clinician and dietitian, general practitioner or no FU. Patients, in this questionnaire based study, preferred a combined clinician and dietitian clinic, although a latter study reported a clear preference for a dietitian only clinic (Ryan et al., 2016). Furthermore, the satisfaction rate in our study shows improvement when compared to our index study (Butterworth et al., 2004) and other similar research (Rubin et al., 1993, Faye et al., 2018). Patient satisfaction, however, is multifactorial and depends on age, receiving an explanation of the symptoms, cause, likely duration and lack of unmet expectations (Jackson et al., 2001). Possible causes for improvement might include improved communication with patients or a response bias in the opinion of the responders (Mazor et al., 2002). Both of the consultations in this study, however, were fulfilling the purpose of the appointment. The important part was the comments left by the patients, who pointed towards certain common issues faced by the patients related to the communication e.g. use of medical jargon, not paying attention to patients' concerns and (above all) poor eye contact. For SA patients, the linguistic barrier was the main issue and previous research recommends the use of the patient's own language (Singh, 2011), although it might not be possible for a variety of training, economic and logistic reasons.

No difference was noted in the dissatisfaction rates of either the Caucasian or SA populations. This again is in contrast to the index study, where SA had more dissatisfaction compared to Caucasians, a finding echoed by another later study (Lyratzopoulos et al., 2012). Additionally, in a slightly different set-up, but with extensive power and robust methodology, a relatively recent study also reported less satisfaction of SA patients with GP consultations (Brodie et al., 2016) and one of the reasons was the linguistic barrier. It may be argued that in our study language support was available, so the result may

have been affected. It is hoped that a clear answer can be found if a large numbers of participants, with modification in the design of the questionnaire, are employed to answer this question i.e. use the ethnic languages for future studies. Additionally, interpretation of patient satisfaction should be adjusted for pertinent patient characteristics (Jackson et al., 2001).

Adherence to a GFD

Our study reported self-reported adherence to a GFD by two methods: absolute adherence to a GFD based on ingestion of any amount of gluten (60.8%) and based on CDAT questionnaire (54.4%). Although absolute adherence is one of the criteria used by the CDAT questionnaire, a validated instrument as compared to Butterworth et al., (2004), it takes into consideration several other social, psychological and symptomatic issues when calculating adherence to a GFD (Leffler et al., 2009). Hence, for the purpose of this PhD, CDAT is the preferred method of estimating adherence to a GFD.

A detailed systematic review by Hall et al., (2009) has reported a wide range of adherence rates and it is affected by the power of the study, age of the patients (Fabiani et al., 2000, Hauser et al., 2006), educational level of the patients (Leffler et al., 2008, Sainsbury et al., 2013b, Villafuerte-Galvez et al., 2015), knowledge (J. Silvester et al., 2016) and methodology of the reported studies. It is, thus, difficult to compare our adherence rate with these studies, keeping in view the multi factorial nature of the studies. An average adherence rate of 58% (range 41% to 91%) reported by Hall and colleagues (2009) is close to our finding.

Studies after Hall et al., (2009) have also reported variable adherence rates. Rajpoot et al., (2015) in a prospective, single-centre, observational study in India (n=172) reported an adherence rate of 53.3%, which is close to our value. The same year, Villafuerte-Galvez et al., (2015) in a US based study (n=709) reported an adherence rate of 75.5% and this is a higher value than in our study. This may be explained by the observation that the participants in this study had been on a GFD for over 10 years and FU had been cited as one of the reasons for better adherence (Rajpoot et al., 2015, Hall et al., 2009, Barratt et al., 2013). The participants in Rajpoot et al., (2015), although all native Indians, were both new and FU patients, which is similar to our cohort. Similarly, Silvester et al., (2016), in a US based study (n=82), reported an adherence rate of 55% which is similar to our value. Although lower powered than our study, this was an adult study with patients under dietitian FU, just as in our cohort. In contrast to this, a higher adherence rate (93%) was reported by a Mexican study (n=1,238) and although an adult study, the striking difference of this study was the increased number of males (45%) and presence of both CD and non-celiac gluten sensitivity patients (Ontiveros et al., 2015), in whom the adherence rate is generally reported to be higher (DiGiacomo et al., 2013). In conclusion, considering our methodology, which was

questionnaire based, our CDAT based adherence value of 54.4% follows previously reported studies to some extent.

Our absolute adherence (60%) as defined by no gluten (except inadvertent intake), is close to the reported value (62%) by Butterworth and colleagues (2004), who used a cohort of mixed ethnicity such as ours. Additionally, it is noteworthy that Butterworth's data was collected a decade earlier than our data and management of CD has changed over those years in the NHS. The nearly static adherence rate, a decade apart with comparatively similar demographics, in two geographically adjacent cities cannot be explained simply by the power difference. One could argue that this may represent a plateau in adherence rate to a GFD, but more research is needed.

The non-adherence group was divided into three groups: mild, moderate and severely non-adherent. Comparing the results, severe non-adherence was noted in 2% of our cohort, as opposed to 18% in the index study (Butterworth et al., 2004). Since the questionnaire, methodology of administration and cohort are comparable, it may be argued that adherence in this group has improved in the past 10 years, although there are differences from the Butterworth study in terms of power and length of FU. Our study presents a comparative picture in a relatively similar cohort and using the same questionnaire.

Things have moved on since 2004 and one may argue that people are now more aware of CD as a disease entity and there has been an increase in the provision of GFP in the shops and online (Burden et al., 2015). It is however possible that the reason behind this improved adherence might be non-response bias, as our sample was comparatively large and the RR was low. It is thus possible that those who responded to the questionnaire were motivated and already more adherent to a GFD. This however needs to be confirmed by performing an audit to measure adherence retrospectively in the dietetics department and comparing the results in order to assess the reliability of our findings.

There was no significant difference between genders when analysed according to adherence rates, although interestingly we noted that all severely non-adherent participants were female. This might simply reflect sample bias, due to the female predominance in the sample (as in any CD sample) (Ivarsson et al., 2000), or this might represent a true trend. Previous studies have referred to the difficulties for women in following a GFD as compared to men (Ciacci et al., 2003, Hallert et al., 2003, Lee & Newman, 2003, Zarkadas et al., 2013), but it is not clear if these difficulties may be translated into severe non-adherence in females. It is thus suggested that a fairly large sample (n>200) of severely

non-adherent patients with histologically proven CD should be surveyed in an attempt to answer this question.

The study did not detect any significant difference based on ethnicity when comparing the non-adherent patients and although this follows the trend as suggested by Hall et al., (2009), the index study (Butterworth et al., 2004) reported opposite results. As previously described, the adherence rate itself has improved and it is possible that the same factor which led to improvement in the adherence rate may also have closed the ethnic gap. In contrast to our findings, a recent UK based study (n=146) reported a significantly low adherence among South Asians to a GFD in comparison to Caucasians (Adam et al., 2019). There are several methodological differences when this study is compared to our study, for example; the study is retrospective, lacks demographic characteristics (age and sex), lack of information about Coeliac UK membership and lack of information about the availability of gluten on prescription. In addition, the study used a non-validated method of classifying patients into three categories; fully adherent, partly adherent (accidental intake) and non-adherent as opposed to our study where CDAT was used, a fully validated and fit for purpose questionnaire. It is thus argued that methodological differences may explain the discrepancy in related results.

It is thought that this question needs further exploration by a combination of research and audits. Similarly, the study did not detect any significant difference based on age of patients when comparing the non-adherent patients and this is in accordance with the conclusion drawn by Hall et al., (2009) from their well-planned systematic review.

Difficulties faced in following a GFD and symptoms post gluten ingestion

The majority of the patients in our study (80%) had concerns about the cost of a GFD, which is indeed expensive. This follows recent research where data was collected from 50 stores and 10 online retailers: it was reported that, although availability of GFP had increased, it was comparatively more expensive than the GCP (Hanci & Jeanes, 2018). Previously, a market based study (Zivin & Green, 2007b) compared similar items (wheat and GF) and found that all 56 GF items were more expensive than their wheat-based counterparts. A relatively more extensive study suggested that GFP were 242% more expensive as compared to gluten-containing equivalents (Stevens & Rashid, 2008b), suggesting the need for GFP to stay on prescription. Our study suggests that the price of GFP, among others, is one factor which significantly affects adherence to a GFD (0.3-1.0. 95% CI, p=0.05).

Although CD patients are not the only consumers of GFP, they were available on prescription on the NHS in England. However, following extensive consultation with different stakeholders, health commissioners across England have implemented changes to restrict access to GFP on prescription to GF breads and flour mixes only (NHS, 2018b), despite an internet based campaign to oppose these changes (Campaign, 2016).

Our study suggests that patients had difficulty understanding GF labelling and this factor was associated significantly with non-adherence. Although understanding of food labelling being a factor for non-adherence was identified in our index study (Butterworth et al., 2004), this trend continues in recent studies as well (Verrill et al., 2013, Sharp et al., 2014). It was not possible to determine exactly how lack of understanding of the labelling was an issue for the patients, but it was clear that this factor was significantly associated with SA, suggesting linguistic or technical barriers. A qualitative research study is needed to explore this point in detail, along with other factors which may affect adherence to a GFD. Additionally, it is suggested that, if the GF food industry included messages on products in major ethnic languages, that might increase understanding and in fact may improve adherence to a GFD. This concept is also linked to restaurant foods being labelled GF whilst actually containing gluten, as suggested by an Irish study which found that 10% of “gluten free” meals in fact contained gluten (McIntosh et al., 2011). Such alarmingly high gluten contents may have multiple causes, but one of them is restaurant chefs’ knowledge about CD. This was examined in a UK based study and it was found to be lower than the general public level of knowledge (Karajeh et al., 2005). However the same group conducted a FU study after a decade (Aziz et al., 2014) and found that GFF food related knowledge had increased significantly in both aforementioned groups; this may well relieve some patients’ concerns around eating out in restaurants. It is suggested that a broad based approach, such as educating both consumers and providers in this industry at all levels, may help this inadvertent ingestion of gluten.

Membership of the CS was one important factor which was significantly associated with increased adherence and this is in accordance with the previously mentioned systematic review (Hall et al., 2009). The CS in the UK (Coeliac UK, 2016c) and other sister organisations or advocacy groups across the globe, provide up-to-date knowledge in patient friendly ways on all major aspects of life as a consumer of a GFD, along with support in following such a diet. How exactly this leads to increased adherence is elusive, although one reason might well be their guidance on GFD (Coeliac UK, 2018), eating out (Coeliac UK, 2016a), food labels (Coeliac UK, 2016b) and gluten sensitivity (Coeliac UK, 2015). It is

also possible to argue that those who are more adherent to a GFD join the CS or an equivalent organisation. If this indeed is the case, then research which inducts patients from such societies (Sainsbury et al., 2013) has selection bias and the results cannot be generalised. One way to examine this issue is to conduct extensive interview based research on members of the CS, both adherent and non-adherent, and explore this area.

Other factors, such as poor palatability of GFP, were reported by our patients and this issue has long been recognised (Thompson, 2009). This factor, which is important from a quality of life point of view as reported earlier (Hall et al., 2009, Olsson et al., 2008), had a significant effect on adherence to a GFD in our study (Table no 9, page 49). Research such as: detoxification of wheat via genetic alteration (Stenman et al., 2009), gluten enzyme degradation (Mitea et al., 2008), volume enhancement with chickpea flour (Bird et al., 2017) and texture enhancement with legumes (Huang et al., 2018) has produced relatively palatable GFP, but this area is evolving and more research is needed.

Another significant factor related to non-adherence in this study was lack of symptoms before the diagnosis. Similarly, factors related to patients' symptoms post gluten ingestion were also significantly related to non-adherence. Although research has shown that there are benefits for both asymptomatic and symptomatic patients from a GFD (Kurppa et al., 2014), it is not exactly clear why non symptomatic patients have reduced adherence, but the answer may be partly explained by the disproportionate drop in quality of life. This was demonstrated in a questionnaire based study, where among asymptomatic patients (n=23), perception of health worsened and concerns about health increased whilst they were on the diet (Ukkola et al., 2011).

Although neither dietitian nor clinician information was associated with adherence to a GFD, being given a contact telephone number by the dietitian was significantly associated with improved adherence in our study. The positive role of a similar strategy has been previously observed in relation to outpatient appointments (Hardy et al., 2001) and obsessive-compulsive disorder (Kenwright et al., 2005), but this was the first time that a study has reported on the positive role of giving telephone contact information to patients and its effect on adherence. Additionally, non-prescription of GFP by the GP was found to be associated with low adherence (Table No 18, page 91). This is especially important in view of the current climate of austerity which has affected GFP prescribing as referred to earlier.

CDAT score and adherence to a GFD and comparison of instruments

Our study has used two methods of assessment for adherence to a GFD (Butterworth and CDAT) and our method of preference is CDAT. There was a significant correlation between increasing CDAT score and non-adherence as measured by Butterworth (p=0.00) and that confirms the previous reported findings (Leffler et al., 2009, Villafuerte-Galvez et al., 2015). This method of measuring adherence is reliable and validated and has been used in multiple recent studies in assessing adherence to a GFD (Villafuerte-Galvez et al., 2015, Mahadev et al., 2013, Nazareth et al., 2015, Haas et al., 2017). Gender and ethnicity of patients had no significant relationship with the adherence as measured by CDAT score, which follows the trend (Butterworth et al., 2004).

Comparing non-adherence, using both Butterworth and Leffler scores, it is clear that Butterworth non-adherence had higher scores, but also that Leffler scores identified more non-adherent patients (54%) as compared to Butterworth (39%); this difference is significant. It is not clear exactly why the Leffler questionnaire is detecting more non-adherent patients, but perhaps it may be explained in terms of questionnaire design. Firstly, the length of a questionnaire may affect the response of individuals (Galesic & Bosnjak, 2009) and in this case may well have affected the quality of data in the Butterworth questionnaire. Secondly, the CDAT score is plotted as continuous variables, ranging from 7 to 35 and giving rise to a compliant (CDAT <13) group and a non-compliant group, whereas the Butterworth score is nominal data and divides the groups into 3 types of non-adherence depending on the interval of gluten ingestion. Although the final question in the Leffler questionnaire also enquires about the adherence of individuals, it generates 4 categories of non-adherent patients, thus giving more choice. Finally, when the data is analysed by two categories in the Leffler questionnaire, the adherence rate is markedly different from the Butterworth questionnaire, but when analysed according to the last question, the adherence rate is comparable in terms of percentage to the Butterworth adherence. This approach may be criticised for the fact that the same cohort was used to compare these questionnaires, which may compel the responder to answer both the questions in the same way and thus affect the quality of the data.

The way to resolve this issue is to administer these questionnaires to different groups who have had a dietitian assessment as a benchmark of their adherence and then draw inference from the questionnaires' ability to measure adherence in these groups. Similarly, membership of the CUK was associated with adherence; this has been explained above in relation to Butterworth adherence. On the

balance of probabilities, it may be argued that the CDAT is more sensitive than the Butterworth questionnaire in detecting non-adherence to a GFD.

This is the first time such a comparison has been reported, by comparing previously used instruments of non-adherence using the same population. The questionnaire design has been discussed in the method section, but it may be relevant to add here that the LQ is shorter, less complex and easier to comprehend. In addition, it has questions about personality traits and draws its validity from multiple recent studies as mentioned above. It is thought that the development of the Leffler was more methodical and took into account the holistic nature of gluten ingestion and not just intake as recalled by the patient. Plus it was developed by a committee of gastroenterologists, dietitians, psychologists and individuals with CD with a validity pilot project and confirmed by blood markers. We thus feel that for future research the LQ should be used and we will follow this suggestion for rest of the PhD.

SECTION IV

Strengths of the study

This study selected a population of CD patients who were diagnosed on objective, highly sensitive and specific grounds i.e. a combination of both serological and histopathological criteria was used. The diagnosis of CD was made by the same pathologists and using the same standards, thus reducing chronology bias. In addition to that, the diagnosis of CD was supplemented from clinical notes, thus the diagnostic sensitivity and specificity was close to 100%. Furthermore, the demographics of the population were compared in terms of age, ethnicity and gender, with a previously reported population in a similar survey targeting patients with CD (Butterworth et al., 2004)

Data reliability

This was a well-designed observational study and data in this study went through a rigorous process of cross checking via an audit, which improved the standard of data for final analysis. Additionally, data was obtained from clinical notes and computerised records which improved the quality, reliability and validity of the data, thus addressing some aspects of data related issues such as recall bias.

Implications of study findings

The findings of this study were published in the journal Nutrients at a time (Muhammad et al.,2017) when public consultation in relation to GFP was at a preliminary stage and our study was cited as one of the strongest pieces of evidence (by NHS England) for a link between prescribing and adherence in their recent document (NHS, 2018a). As a result, this may affect access to GFP for certain patient groups and this may also affect adherence to a GFD, but larger studies are needed to explore this point of immense practical importance.

This study evaluated a single English NHS Trust and found no major differences in the patient perceived management of CD in White and SA populations. Our Index study painted a different picture, where SA patients were being treated sub-optimally. The Index study, however, was published in 2004 and the data therein is at least 14 years old. It is possible that their findings were isolated, but it is also possible that the suggestions made in the study have changed attitudes towards Asian minorities and thus improved health care for that group. If treated as a FU study, this study shows that patient education

has improved in relation to CD patients. However, SA are still not receiving adequate information to enable them to understand food labels -which is key to adherence.

The ultimate aim of measuring adherence to a GFD is to find ways to increase adherence in the future, which will help to prevent long-term complications of CD. A team effort from physicians and dietitians is needed and, although it might appear difficult to improve patient adherence, it is not unachievable. This study may help to alleviate the difficulties associated with following a GFD by increasing awareness in both patients and physicians.

Limitations of the research

There were several limitations which might have affected the quality of this research. Firstly, the choice of a questionnaire (Bowling, 2005) and additionally sampling may be selective (Andrews et al., 2003). Data quality is a relative construct and depends on multiple factors, but it is accepted that sampling may be biased in questionnaire based studies. However it should be noted that Andrew and colleagues conducted their research in relation to an internet based survey, which differs from mail surveys in terms of its penetration and access to the experimental cohort (Kaplowitz et al., 2004).

Secondly, the survey may be affected by RR and that is why every effort was made to increase the RR in the light of research (Richards, 2007, Edwards et al., 2009, Root & Blismas, 2003), although it is accepted that RR is on the decline in mail based surveys (Galea & Tracy, 2007). This study achieved a RR of 38.5% and, although there are no good or bad RRs (Richardson, 2005), this rate is on the lower end of acceptability (Gehlbach, 2006). As a result, it may be argued that the collected data may have been affected by non-response bias (Hill et al., 1997), although rates as low as 20% may still be valid and accurate in relation to data quality as suggested by (Visser et al., 1996), or in other words low RR is not synonymous with non-accurate results, as suggested by a few authors (Holbrook et al., 2007, Keeter et al., 2006, Curtin et al., 2000). The notion of dissociating quality of research from the RR is further supported by a study comparing relative risk estimation from two studies with different RRs yet comparable and consistent results (Mealing et al., 2010). Also, a meta-analysis has suggested that detailed description of methodology and the way data was collected is more predictable in determining quality of data than RR (Cook et al., 2000). Additionally, despite the low adherence rates, there may be some selection bias, since the participants who responded may be more motivated and perhaps therefore more likely to adhere to a GFD.

Thirdly, it is accepted that the questionnaire method of survey excludes certain groups such as blind and visually impaired people, as special arrangements were not in place (such as the tactile reading system, Braille (Kaczmarski & Wolff, 2007) or audio supported questionnaires (Kirchner & Schmeidler, 2001)). However there are no clear reports on the prevalence of visually impaired patients with CD, apart from scattered case reports and secondary references in articles (Millington et al., 2015, Lea et al., 1995, Pfaender et al., 2004). Another group which might have been excluded would be those with literacy problems and elderly patients who may have health and/or computer literacy issues. Although support in 7 ethnic languages was available from the author, it is possible that patients of languages outside the list provided might have been excluded.

Fourthly, questionnaire based methodology is static and does not carry lateral or longitudinal depth of exploration (Coughlan et al., 2009). However it must be noted that the purpose of this piece of research was not an in-depth enquiry into CD; rather it was a valid questionnaire designed for collecting pre-determined data.

Fifthly, the questionnaire RR was 38.5% which, whilst low, compares well with other similar published studies. Also, all the questionnaires were completed and the entries were legible. Furthermore, separate themes were extracted from the added comments and that gave an extra dimension to the issues raised by the patients. Finally, although adherence was measured through a questionnaire based methodology, there was no external verification such as histology (Ensari, 2016, Villanacci, 2015) or a combination of serology with histology. Additionally, by the time this research was being conducted, novel methods of ascertaining adherence were in development, such as urinary markers (Comino et al., 2012, Moreno et al., 2017) for CD. It is suggested that in future, if measurement of adherence is being researched, especially in relation to an intervention, it may be supplemented with laboratory data to increase the validity of the study findings.

Conclusion & future research

The CD database provides a unique opportunity to evaluate: the adherence rate to a GFD, causes behind low adherence to a GFD and reliable incidence and prevalence rates of CD in the Leicestershire area. Keeping the aforementioned limitations in view, this study has certainly established that adherence to GFD is related to food labelling, membership of the CS and cost and texture of GFF. This study, however, found no major difference in adherence to a GFD between the Caucasian and SA populations;

this is contrary to the index study (Butterworth et al; 2005), where Asians were reported to be less adherent. This may be because of increased awareness about GFD among Asian patients, but a large scale interview based research study could confirm this finding.

Extending this study would be feasible with more participants, employing mixed methods of delivery, additional questionnaires and supplementing information provided by the patients with clinical letters and computerised data. The study findings must be interpreted with caution and must be taken in context. The author also recommends that current literature and local trends must be taken into consideration before applying the findings of this study to similar groups or set-ups. It should thus be treated as a baseline study for the purpose of providing ideas about adherence rates and basic demographics of CD.

The main lesson from this study is perhaps that adherence rates in the Leicestershire area are very close to the national average and there are definitive reasons behind that including: cost of GFF, taste of GFP and reading food labels correctly. Addressing these reasons will include educating patients about food labelling, encouraging joining the CS and, last but not least, providing them with support when needed to bring the daily transgressors to absolute adherence, by repeated counselling in dedicated CD clinics.

Another related and important finding is the correlation between adherence with membership of the CS or other advocacy groups. This theme has been reported in several studies (Butterworth et al., 2004, Hall et al., 2009, Charalampopoulos et al., 2013, Sdepanian et al., 2001) and in my MSc pilot study (Muhammad et al 2013). It is not clear what exactly leads to increased adherence, but possible explanations might well be: group therapy, increased education about CD, timely advice about diet, regular leaflets and emails. However, more questionnaire or interview based research is needed to fully evaluate this area.

Chapter Three

Study 2 (PhD): Patients' Views on Improving Adherence to a Gluten Free Diet in Coeliac Disease (Your View)

SECTION I

Introduction:

Non adherence to a GFD ranges from 53 to 76% (Hall et al., 2013, Villafuerte-Galvez et al., 2015, Casellas et al., 2015, Rajpoot et al., 2015, Sainsbury et al., 2018), which may cause persistent symptoms (Dewar et al., 2012). Behavioural change is a key factor in improving the implementation of evidence based interventions to increase adherence to a GFD (Sainsbury, Mullan & Sharpe, 2013b). It may be defined as "coordinated sets of activities designed to change specified behaviour patterns" (Michie et al., 2011) and in the case of adherence to a GFD, it means reduced or no intake of gluten. Research has indicated that non-adherence to a GFD is multifactorial (Hall et al., 2009) and improved adherence to a GFD has beneficial effects on the activity and associated complications of CD (Whitaker et al., 2009, Siniscalchi et al., 2005b, Kotze, 2004). Different instruments have been used to measure gluten intake and these have been reviewed in chapter 1. There exists a gap in knowledge in relation to factors influencing dietary adherence in South Asian people. There are quantitative studies with variable methodologies (reviewed earlier page No 53) which has explored this area but to date there are no in depth qualitative studies. The reason for this seems multifactorial including; cultural and linguistic barriers and interview based research are needed to explore this area.

Study Aims:

1. Explore reasons for non-adherence
2. Explore options for interventions to promote adherence to GF diet

Method:

This was a short semi-structured telephonic interview, conducted in two phases, which on average lasted for 20 to 30 minutes and for which guidance was drawn from different sources (Carr & Worth, 2001, Valenzuela & Shrivastava, 2002, Britten, 1995, DiCicco-Bloom & Crabtree, 2006, Turner III, 2010, Burke & Miller, 2001).

It was fit for purpose in exploring patients' views about the design of an intervention to promote GF dietary adherence (Harvey, 1988) and causes for non-adherence. The interview was conducted according to a topic guide (Appendix 1.3E) which served as a formal structure for conducting the interview, although it is acknowledged that a topic guide does not provide a rigid structure; such interviews are flexible and open to accepting respondents' spontaneous descriptions and narratives (Brinkmann, 2014). The completed interviews were recorded, transcribed and then codified using qualitative techniques and the data was subsequently analysed.

Participants:

The participants in the study came from a subset of the CD database held within the UHL pathology department and they were the responders in Study 1 (Chapter 2). Only those who were diagnosed between 2004 and 2014 were eligible state diagnostic bits. Demographic records were checked using the Trust's computerised diagnostic software, ILAB® (2nd Edition, 2010).

Inclusion Criteria:

Patients who responded to the questionnaire in study one were eligible for inclusion in this study. All patients were 18 years or above and had histologically confirmed CD. As per study one, only patients who were diagnosed by UHL pathologists and were under UHL follow up, were included.

Exclusion Criteria:

All patients who had not responded to study one were excluded. In addition to that, all those patients who were not under UHL follow up were excluded, as the local Research and Development office approval was only applicable to current UHL patients. Those who were finally selected were divided into 2 groups: adherent and non-adherent, based on the findings of study one.

Questions in Telephonic Interview

Each interview question was designed to clearly address a single topic and guidance was drawn from previous research and suggestions (Babbie, 1989, DiCicco-Bloom & Crabtree, 2006, Turner III, 2010). In addition, an evidence based approach was adopted when designing the questions to ensure objectivity. This included: literature search, in-depth reading of the topic being researched, opinions of experts in the field and avoiding difficult and unanswerable questions or questions which had already

been answered (Robson, 2002, DiCicco-Bloom & Crabtree, 2006). The interview opened with a formal introduction, where the patient was identified by simple questions and the purpose of the interview was reiterated. Similarly the first couple of minutes were utilised to build *rapport* with the patient (Price et al., 2012), followed by specific questions. Different types of questions used in the interview are given in the table below (Table No 29).

Table 29: Themes and question types in the interview

Themes	Question type
Exploring issues	Main issues preventing following a GFD
Exploring obstacles	Specific obstacles preventing following a GFD
Exploring specific problems	Specific problems in following a GFD
Exploring factors	Specific factors preventing following a GFD
Exploring reasons	Reasons which prevent following a GFD

The above questions generated factors responsible for difficulties following a GFD and the patients were then asked about the possible modifiable factors which could be improved and lead to adherence to a GFD. This was mainly a listening area, where patients came up with their own methodologies for dealing with modifiable factors. Thereafter, the researcher was involved actively and asked a series of follow up questions to clear up any ambiguities, as suggested by previous research (Sturges & Hanrahan, 2004), such as probing (Rubin & Rubin, 2011) and specific question (Legard et al., 2003). Subsequently, a series of direct and indirect questions were asked to further probe the specific area and they are given in the table below (Table No 30).

Table 30: Types of questions in the interview

Direct Questions	Indirect Questions
Is adherence to a GFD important for you?	What is your opinion on following a GFD?
Is it possible to improve adherence to a GFD?	Should people follow a GFD or it is an option?
Any plans to improve adherence to a GFD?	Is a GFD important for asymptomatic CD patients?
Are you ready to improve adherence?	What is your opinion on GFD transgression?
Have you already started working on it?	What is the possible solution to following a GFD?
Do you need any help in this regard?	Can you follow a GFD on your own?
How many times a month might you take gluten?	Is a GFD absolute or a relatively optional diet?

Interview questions generated further spontaneous themes and as new themes came to surface questioning techniques and strategies were changed accordingly until the point that theme saturation was reached (Francis et al., 2010, Tong et al., 2007, Walker, 2012). The interviews were recorded using the call recorder® app and the Record app of the IPhone 5. The data obtained was directly entered into interview transcripts.

Procedure:

Each participant was given a unique trial number, which was assigned by the principle investigator to preserve confidentiality of the patients. This was stamped on every document using a COLOP® mini-folio (S126) prefilled number generating stamp. The research pack (contained in a C5 envelope) included an invitation letter, patient information sheet, consent form and patient's availability calendar, along with a stamped addressed envelope (Appendices 1.2 A-D). Using an online randomising interface for researchers, randomisation was conducted to select patients (Randomiser, 2016). The details of this process is given in the result section below (Section II, Pages No 136-38).

Conduct of the Study:

As a first step, participants (n=15) were randomly selected from the responder group and pilot interviews (n=13) were conducted. All the patients in this phase were adherent to a GFD and the details of the demographics are given in the result section. This was done to gather data to refine the topic guide for actual interviews. None of the data generated in these initial interviews was used for the final analysis. Patients were informed that their data would not be used in the analysis, but would aid the research

tremendously by helping to improve the topic guide which would standardise the research. This approach guided the author towards rapport and wording issues and also helped with the timing of the interview. Although, care was taken to conduct these pilot interviews by including participants who were demographically similar to the rest of the cohort, it was not possible in all respects. A thorough process of reflection was then allowed after each interview to refine questioning technique and rapport building; necessary changes were made to the topic guide accordingly.

A separate leaflet in seven ethnic languages accompanied the invitation letter, welcoming questions from anybody who had difficulty understanding the purpose or conduct of the study.. The researcher received a total of 20 calls from different patients and a clear majority (n=15) were referring to a mistake in the timings on the patient calendar. They were given guidance and no further calls were received in this regard. The remaining calls were about general aspects of research such as the purpose of the research, and one patient updated her new address. All of those who made enquiries were satisfied with the explanations given.

Ethics:

Integrated Research Application System (IRAS) was used to apply for ethical approval for the study (IRAS ID: 177503). The study was first approved by the procedures of the University of Roehampton Ethics Committee (LCS 15/130). Ethical approval was then applied for through the central NHS Research and Ethics Committee (REC) and permission was granted from the REC Yorkshire & The Humber-Sheffield (Ref: 15/YH/0289). The local NHS research and development department at UHL was involved through a site specific application form linked to IRAS (UHL 11418). The details of ethical approval are attached as an appendices 2.2A-D.

Data Analysis:

Several software programmes are available to analyse qualitative data, such as: Aquad, CLAN, NVivo, ATLAS-ti and others; all have their merits and demerits. For this project, data was analysed in NVIVO® version 11, which is Windows® based qualitative data analysis software (Bazeley & Jackson, 2013) and its use is well established in qualitative analysis (Bringer et al., 2004, Walsh, 2003). There are several advantages of NVIVO® including: it may be used in both qualitative and mixed methods research and designed to organise, analyse and find insights in unstructured or qualitative data. In addition to that, it also helps index segments of text to particular themes; link research notes to coding; carry out complex

search and retrieve operations and aid the researcher in examining possible relationships between themes (King et al., 2004).

Quantitative data generated from this study was analysed using SPSS® version 24. Descriptive statistics were computed for mean, mode, standard deviation (SD) and associated kurtosis and skewness. Normality of the data was assessed by Kolmogorov–Smirnov test (K–S test). Ethnicity and gender were compared with Chi-Square test ($\chi 2$ test) in 2X2 contingency tables. For the analysis of continuous variables such as age or CDAT Score, Student's t-test was employed or Mann–Whitney U test if parametric assumptions were not met. In all instances a statistical value of $P = 0.05$ or lower was considered significant.

Theme analysis:

The sources of the data were interview transcripts and field notes. The transcribed scripts were approached in a systematic way and themes and issues addressed in the interviews were linked to each other via a category system. A constant comparative method of analysis (Boeije, 2002) was used where different segments such as line, paragraph and sentences were codified in the light of field notes. First of all, notes were made after each interview to supplement the recording and they were the spontaneous thoughts of the author after each interview, with guidance from previous works (Maxwell, 2012, Strauss & Corbin, 1990). Following this, all transcripts were skimmed to ''sense'' the data in terms of volume and diversity and then a systematic reading was given to identify different aspects of the contents (Morse & Field, 1995). Following this, based on theory or available data, "open coding" was done as per guidance from previous research (Flick, 2009) and as shown in Figure below (Fig No 13).

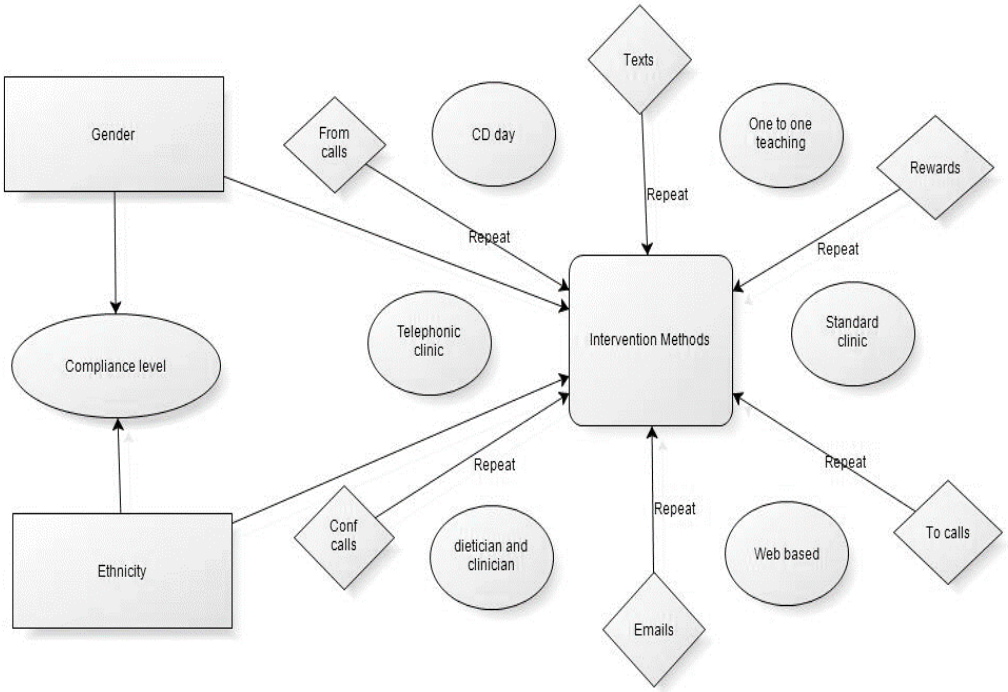

Figure 13: Interview process to refine the nodes and themes

The codes were divided into different categories by asking questions in relation to nodes. Questions such as: “what is this?”, “why is this interesting?” and “is this relevant to the research question?” generated descriptive, thematic and analytic categories of nodes respectively (Bazeley & Jackson, 2013). The structure of data organisation and its basis is shown in the diagram below (Fig No 14).

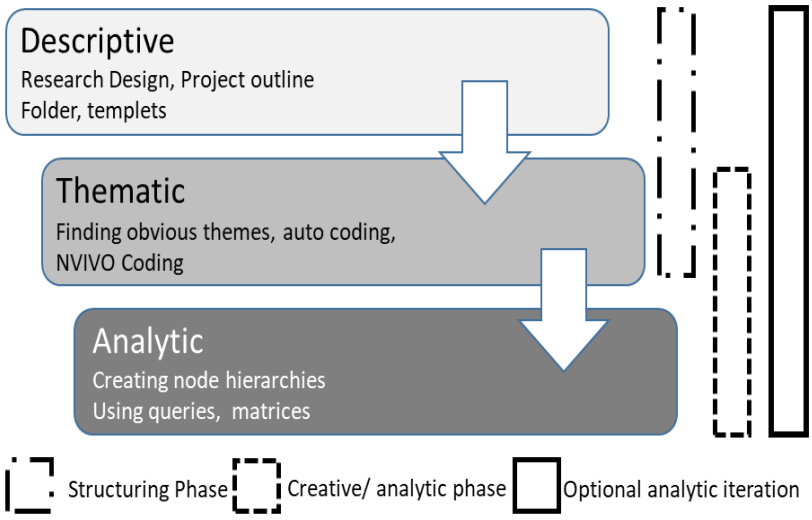

Figure 14: Data organisation. Adapted NVivo® 11 Essentials by Edhlund & McDougall, 2016

Help was also obtained from the auto coding feature of the NVIVO®. Subsequently higher orders were identified in the open codes and the aim here was to condense the data to avoid unnecessary repetition. Then the data was reviewed in order to identify similarities between themes, generalisation trends, inter-code relationships and differences, to generate a set of conclusions which would help to develop theories or test hypotheses. Codes were subjected to queries and annotation using NVIVO® to extract meaningful directions from the data analysed (Bazeley & Jackson, 2013). The suggested structural hierarchy of the analysis is given in the diagram below (Fig No 15).

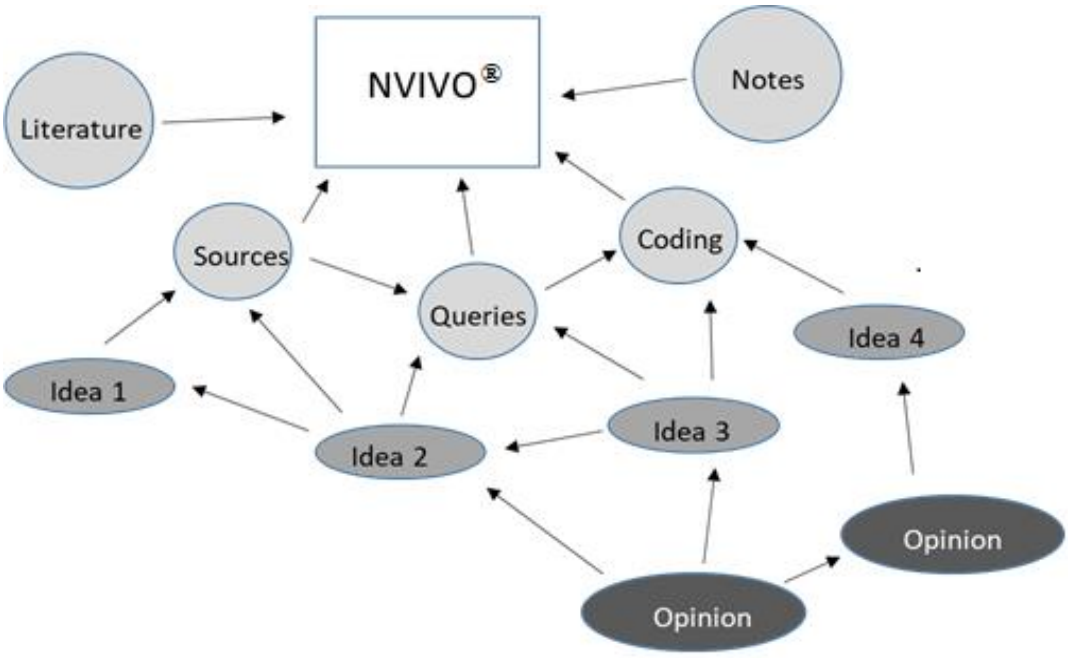

Figure 15: structural hierarchy of the analysis

Comparative analysis:

Patients were asked specific questions during the interview to compare: cost effectiveness, usefulness, behaviour modification potential, knowledge potential and over effectiveness of different techniques. A simple Likert scale (Likert, 1932) was used to record their opinions. The table below shows the pattern used during the interview (Table No 31).

Table 31: Question types in interview

Direct Questions	Indirect Questions
Cost incurred to mode of intervention	1--2--3--4-5--6--7--8--9--10
Usefulness of mode of intervention	1--2--3--4-5--6--7--8--9--10
Effect on knowledge of mode of intervention	1--2--3--4-5--6--7--8--9--10
Behavioural modification potential of mode of intervention	1--2--3--4-5--6--7--8--9--10
Overall effectivity of mode of intervention	**1--2--3--4-5--6--7--8--9--10**

Next, patients were asked about the type of incentive they would prefer to help them remain adherent to a GFD. This included categories such as: holidays, monetary incentives, GF food hampers, gift vouchers or something else. It was however specified that incentives which had monetary value or were expensive maybe available in limited numbers, but GF food hampers might well be available in high numbers, thus increasing their chances of winning.

SECTION II

Results:

Participant selection process

Thirty seven patients were selected through a process of randomisation and selection which had several phases and none of the patients found the interview objectionable or found any aspect of it sensitive enough to cut the interview short (Mealer & Jones, 2014). In the first phase, the responder group (n=375) of Study 1 of the PhD ("No Triticeae") was selected. In addition, an extra 21 patients were also available who had replied late and seven of them were non-adherent. Only the non-adherent (n=7) from this group were added to the 375 for final possible participation in the study and this made available a total of 382 participants. The age of the population ranged from 18 to 85 years (Mdn = 49, IQR = 33-60). This was a White Caucasian and female predominant group and had 343 (89.8%) White Caucasians and 267 (70.7%) females whereas the age of the female sub-group was significantly higher than the male counterparts: $U = 11508$, $z = -3.88$, $p < 0.01$, $r = -.19$. CDAT Scores ranged from 7 to 30 (Mdn = 13, IQR=13-19). (Appendix 4.2Aa-d).

In the next phase, 255 patients were selected randomly from the above cohort (n=382); they were divided into adherent and non-adherent groups. The ages of the population ranged from 18 to 85 years (Mdn = 48, IQR=32-59). The population was predominantly white females (59.6%), the randomisation increased the number of males from 30% to 32% and reduced the females from 70% to 68% (NS). Total CDAT Scores for the population (n=255) ranged from 7 to 30 (Mdn = 16, IQR=11-20). There were 82 patients whose CDAT score was above 13 and non-adherent according to Leffler's questionnaire and there was no significant difference between male and female participants in relation to adherence to GFD (Leffler et al., 2009) (Appendices 4.2Ba-e).

Postal invitations were sent to 255 pts and 135 of the invitations were accepted, giving a return rate of 53%. All patients filled the patient calendar with clear information about possible dates and timings for the interview, along with a contact number. 53.5% of the 155 non-adherent patients responded and accepted the invitation; 52% of the 100 adherent patients responded.

The ages of the population (n=135) ranged from 18 to 82 years (Mdn = 44, IQR=31-57) and CDAT Scores for the population ranged from 7 to 30 (Mdn = 16, IQR=12-20). There were 40 (29.6%) patients whose score was above 13 and non-adherent according to Leffler's questionnaire. At all levels of selection and randomisation, there were no significant differences in age, gender and ethnicity (table 32). (Appendices 4.2Ca-g).

Table 32: Different phases towards final selection of patients for interview

	Phase 1 (From study I)				Phase 2 (Randomisation)				Phase 3 (Responders)			
	Total (n=382)	**Randomised** 255 (66.8 %)	**Non-Randomised** 127 (32.2%)	***p***	**Total** (n=255)	**Adherent** 100 (39.2 %)	**Non-adherent** 155 (60.8%)	***p***	**Total** (n=135)	**Adherent** 52 (39.2 %)	**Non-adherent** 83 (60.8%)	***p***
Mdn CDAT (IQR)	13 (10-19)	16 (11-20)	10 (8-13)		16 (11-20)	11 (9-13)	19 (16-22)		16 (12-20)	12 (9-13)	20 (16-22)	
Mdn Age (IQR)	49 (33-60)	48 (32-59)	51 (33-62)	.32*	48 (32-59)	51 (32-60)	46 (33-59)	.55*	44 (31-57)	45 (31-59)	43 (31-56)	.43***
Males	115 (30.1%)	82 (21.5%)	33 (8.6%)	.21**	82 (32.2%)	29 (11.4%)	53 (20.8%)	.38**	45 (33.3%)	15 (11.1%)	30 (22.2%)	.38**
Females	267 (70.7%)	173 (45.3%)	94 (24.6%)		173 (67.8%)	71 (27.8%)	102 (40.0%)		90 (66.7%)	37 (27.4%)	53 (39.3%)	
White Caucasians	343 (89.8%)	227 (84.4%)	116 (30.4%)	.48**	227 (89.0%)	89 (34.9%)	138 (54.1%)	.99**	116 (85.9%)	44 (32.6%)	72 (53.3%)	.72**
South Asians	39 (10.2%)	28 (15.2%)	11 (2.9%)		28 (11.0%)	11 (4.3%)	17 (6.7%)		19 (14.1%)	8 (5.9%)	11 (8.1%)	

***Mann Whitney U test, **Chi Square test, ***Independent sample *t* test**

Selection of the patients to interview:

Since the number of responders (n=135) exceeded the number of intended interviews (n=52), 80 participants were randomly selected (described below) from the responders, by first dividing them into adherent (n=52) and non-adherent groups (n=83) and then separately randomising them. It was estimated that 20 interviews would be sufficient from the former group, so by random selection 20 participants were selected (Guest et al., 2006a). Similarly, 60 participants were randomly selected from the non-adherent group. A total of 52 interviews were planned to be conducted based on theme saturation, 15 were for the pilot study and 37 were included within the analysis.

Those who were not included in the interview were individually called to thank them for their help with the research; the author apologised for not conducting their interviews, explaining that the required number of interviews had already been conducted. The figure below shows the staged approach towards final selection of individual participants for the interviews (Fig No 16).

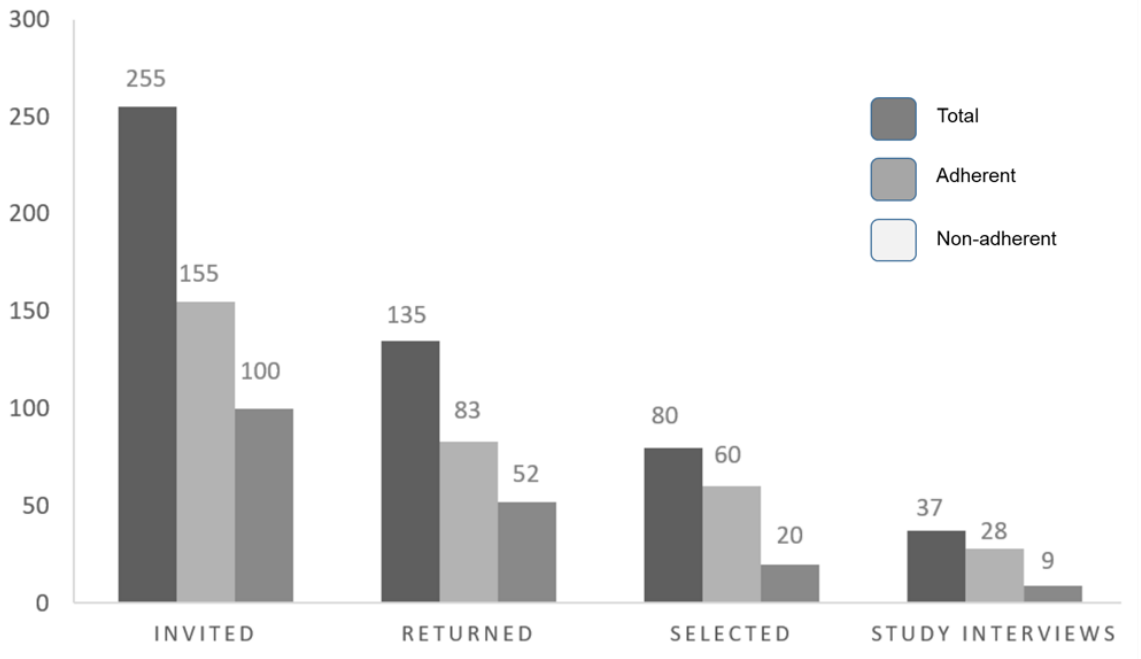

Figure 16: Bar chart showing the selected and interviewed populations.

Demographics of the pilot interview group:

As explained earlier 15 adherent participants were randomly selected from those patients who accepted the interview invitation (n=135) for pilot interview and out of them 13 were interviewed to refine the topic guide. The age of the population (n=13) ranged from 32 to 68 years (Mdn =53, IQR= 43-59) and it was

normally distributed. There were nine females in this interviewed group. Additionally, there were two South Asians in the group and the remaining were White Caucasians. Furthermore, there were 10 patients who were adherent to GFD in this group. The CDAT score of this group ranged from 10 to 16 and it was not distributed normally (Mdn=13, IQR= 10-16). Six interviews were conducted in international languages (3 Hindi/Urdu and 3 in Punjabi) and the remaining were conducted in English.

Demographics of the finally interviewed group:

The age of the study population (n=37) ranged from 19 to 77 years (M = 43, SD = 15.2). The gender and ethnic distributions of the populations of pre and post randomised samples were compared and are shown in the Table below (Table No 33).

Table 33: Characteristics of the adherent and non-adherent groups.

		Adherence to a GFD		
Variables	**Total**	**Adherent**	**Non-adherent**	***P* Value**
	n=37	9 (39.2 %)	28 (60.8%)	
Mean Age ± SD	43± 15.2	43.4 ± 17.3	42.8 ± 14.8	.61*
Age Groups				
< 20 years	1 (2.7%)	-- (--%)	1 (2.7%)	
21 -30 years	9 (24.3%)	3 (8.1%)	6 (16.2%)	
30-40 years	5 (13.5%)	1 (2.7%)	4 (10.8%)	
41-50 years	12 (32.4%)	2 (5.4%)	10 (27.0%)	
51-6- years	4 (10.8%)	2 (5.4%)	2 (5.4%)	
61-70 years	4 (10.8%)	-- (--%)	4 (10.8%)	
> 70 years	2 (5.4%)	1 (2.7%)	1 (2.7%)	
Gender				.056**
Male	8 (21.6%)	4 (10.8%)	4 (10.8%)	
Female	29 (78.4%)	5 (13.5%)	24 (64.9%)	
Ethnicity				.86**
White Caucasians	28 (75.7%)	7 (18.9%)	21 (56.8%)	
South Asians	9 (24.3%)	2 (5.4%)	7 (18.9%)	

***Independent sample T test, **Chi Square test**

The table above shows there was no significant difference between the ages of adherent (M=43.4, SD=17.3) and non-adherent (M42.8, SD=14.8) patients, Conditions; t (35) =-.099, p=.92. Likewise there were no significant differences between the genders, χ2 (1, n=37) =3.65, p=.056, phi = -.31 or ethnicities, χ2 (1, n=37) = .029, p=.86, phi = -.02 (Appendices 4.2Da-d)

The number of absolute non-adherent patients, who were ingesting gluten on a daily basis in this group was 7 (5.5 %), followed by 25.1% who were ingesting gluten on a weekly basis. The table below shows the self-reported gluten ingestion of the population (Table No 34).

Table 34 : Ingestion of gluten in the study population.

	Ingestion of Gluten				
	Adherent (n=9)		**Non Adherent (n=28)**		
Frequency	**Frequency**	**Percentage**	**Frequency**	**Percentage**	**Total**
Never	9	100%	0	0.0%	**9 (24.3%)**
Daily	0	0	1	3.6%	**1 (2.7%)**
Once a week	0	0	8	28.6%	**8(21.6%)**
Once a month	0	0	18	64.3%	**18 (48.6%)**
rarely	0	0	1	3.6%	**1 (2.7%)**
Total	**9**	**24.4%**	**28**	**75.6%**	**37**

Total CDAT Scores for the population (n=37) ranged from 9 to 29 (M = 18.3, SD = 5.8). The scores were distributed normally (p=0.00), with skewness of .28 (SE = .38) and kurtosis of -.91 (SE = .75). The frequencies of CDAT score are shown in the line chart with a superimposed normal curve (Fig No 17) (Appendix 4.2De)

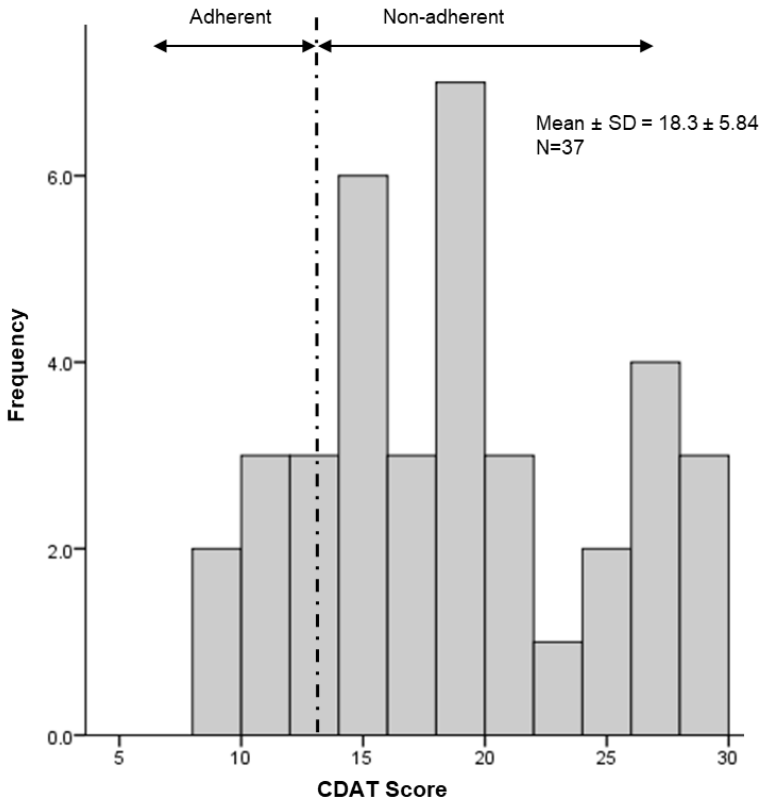

Figure 17: CDAT scores of the interviewed sample. Line shows the cut off score and to the left (<13) is the adherent group.

SECTION III

Study Interviews

A total of 37 participants were interviewed, as at this point themes were saturated and no further interviews were conducted thereafter (Guest et al., 2006b). It was a predominantly White Caucasian sample with a female predominance. The number of Caucasians was 28 (76%) and there were 29 (78%) females in the interviewed group. Interviews lasted for up to 30 minutes. All non-adherent participants wanted to increase their adherence, which meant that they were not on the initial phase of the trans-theoretical model of behaviour change (Prochaska et al., 2008), where people have not thought about changing their behaviour as yet.

Theme analysis:

The most common words in the interviews were first detected through a word query and the most common word was “Researcher” followed by the word “Patient”. This was used in the generation of nodes for further analysis. The word cloud of all the transcripts is shown in the figure below (Fig No 18).

Figure 18: Word Cloud of all transcripts in the study.

Following this, main nodes were generated by going through each transcript; they were classified into main themes from A to S based on relevance to the theme and research question. This step generated 19 main nodes, where the most common theme was CD clinics, which had 37 sources and 324

references. The word “adherence” had 28 sources and 188 references. Main nodes and their relative frequencies are displayed in the table below (Table No 35).

Table 35: Classification of nodes in the main stem.

Node Type	Sources	References	Classification
Adherence	28	188	Thematic, Analytic
Belief and GFD	12	33	Thematic, Analytic
CD Clinics	37	324	Thematic, Analytic
CD Diagnosis	7	7	Descriptive
Complication of CD	12	25	Descriptive, Analytic
Cost and GFD	1	2	Descriptive, Analytic
Demographics	0	0	Descriptive
Hospital and CD	0	0	Thematic, Analytic
Cultural Perceptions	3	3	Thematic
Dietitian Appointment	12	12	Thematic, Analytic
CD Knowledge	10	11	Descriptive, Analytic
Gluten Free Diet	37	37	Descriptive, Analytic, Thematic
Mode of Intervention	3	6	Descriptive, Analytic, Thematic
GFD on Prescription	8	9	Descriptive, Analytic
Problem following GFD	2	3	Thematic, Analytic
Restaurant and GFD	5	7	Thematic, Analytic
Rewards and Adherence	0	0	Descriptive
Shopping and GFD	8	9	Descriptive
Miscellaneous	0	0	Descriptive, Analytic, Thematic

Adherence to a GFD*:*

This appeared in 28 nodes and 188 references; several sub themes were identified among the nodes and references. The figure below gives details of this and related nodes (Fig No 19).

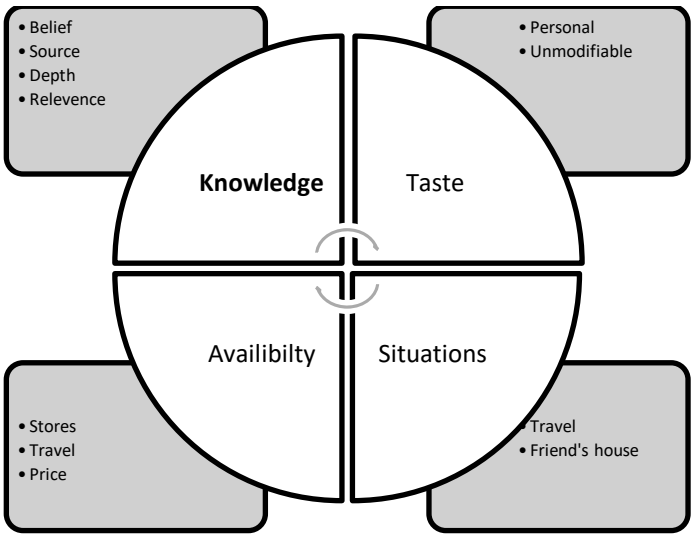

Figure 19: Main nodes and related themes in relation to adherence to a GFD.

One of the principle sub themes was if adherence was possible at all and 26 out of 28 responded yes. Similarly 22 out of 28 were of the opinion that a GFD could be adapted.

Several factors (Nodes=41) were identified which could possibly lead to low adherence in the population. These were broadly classified into lack of knowledge (Nodes=13, References=36), finding themselves in situations leading to low adherence (Nodes=2, References=2), unacceptable taste (Nodes=2, References=2) and lack of variety in GF products (Nodes=1, References=36). Additionally, availability of GF products, either on prescription or in local stores, was related to the main theme of adherence to a GFD. Furthermore there were special situations e.g. travelling or dining at a friend's house, which lead to non-adherence to a GFD.

Knowledge about a GFD was based on belief about the necessity of adherence to a GFD (Nodes=37, References=108) and beliefs about a GFD itself (Nodes=12, References=33). In the former category, theme analysis revealed that 16 participants (57%) from the non-adherent group did not consider it important or necessary to adopt an absolute GFD. Generally, being symptom free was one factor in non-adherence to a GFD, as suggested by a patient:

"…. but you see, I don't think it is an important element in controlling the disease activity especially if I haven't got any issue with that…." (CD2/001, F, 21 years)

The latter category included beliefs about the cultural and nutritional importance of gluten i.e. bread and it was given a central role in the diet as suggested by a patient:

"I ate rice for a few weeks but then you cannot eat rice all your life, can you? (CD2, 013, F, age 34) *and "wheat is an essential part of our culture.. Something we have been doing for centuries.. How can that be an issue when our forefathers have done something for years and now it suddenly became an issue* (CD2, 011, F, age 23).

One patient refused that he would ever be able to adapt his diet based on his culture and the other referred to religious issues;

"The diet does not fit in our cultural aspect." (CD2, 010, F, age 49), "*…it is a matter of religion after all… what to eat and what not to eat…*(CD2, 012, M, age 42).

A dominant majority (22/28) were able to consider adapting strict adherence provided they had information about this subject. Linked to this concept, knowledge about a GFD was related to CD knowledge (Nodes=37, References=368) and that had many sources including: hospital dietitians, family and friends, patients with CD, social media and clinicians. This was further related to knowledge about complications of CD (Nodes=12, References= 25). Knowledge about complications of CD was one area where patients lacked a degree of insight and this was gathered under a single node (Nodes=12, References= 25). There were sub nodes such as: bone health complications, complications of CD in relation to cancer and haematological complications of CD. Theme analysis showed that 23/28 patients lacked knowledge about these complications. The overall theme analysis showed that improving knowledge may lead to improvement in adherence to a GFD. The figure below shows the interrelation of these nodes and possible related effects of low adherence to a GFD (Fig No 20).

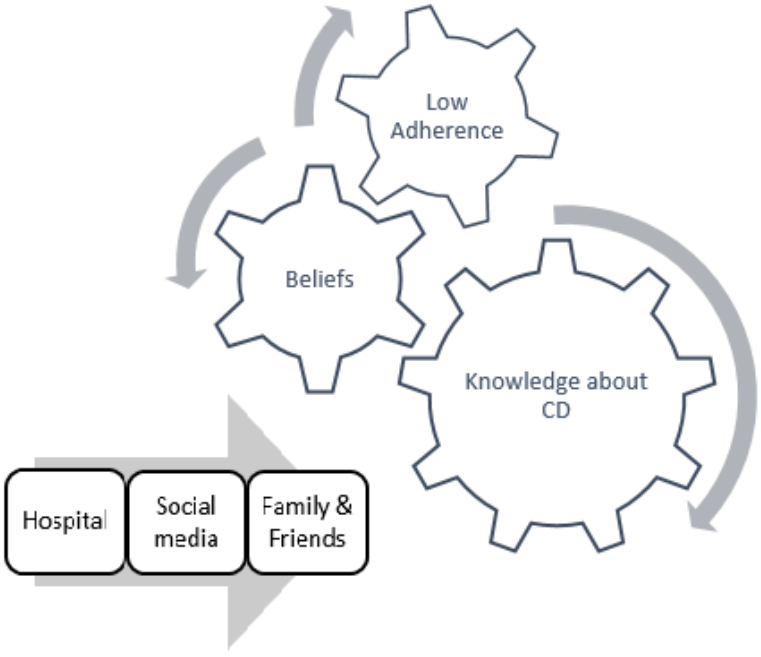

Figure 20: CD and GFD related knowledge.

The taste of GF products was featured in nodes (n=2) and sub nodes (n=2) i.e. adherence to a GFD, cultural perceptions about a GFD, issues with a GFD and the restrictive nature of a GFD. A total of 16/28 participants had issues with the taste of GF products.

"Gluten free products have no taste (CD02/001, F, Age 21), *"…and has no taste…"* (CD02/010, F, Age 49), *"tastes bad and smells.. Don't want to say .. But I don't like it.* (CD02/018, M, Age 56), *"it is not a palatable a diet you see… I like my bread.."* (CD02/020, M, Age 29), *and "taste is not good either"* (CD02/023, F, Age 42).

Furthermore, several nodes (n=5) were related to availability of GF products: Shopping and GFD, Prescription and GFD, Problems following a GFD, Restaurant and GFD. Local stores in Asian quarters were not selling GF products as acknowledged by all of the Asian patients. In contrast GF foods were available in major supermarkets. Theme analysis showed that, lack of availability of GFD (n=11) had negative impact on the adherence to GFD. Finally, there were two important situations (travelling and visiting a friend's house) which posed special issues with following a GFD. Patients commented that it was difficult to obtain GF products (n=11), they felt embarrassed when asking for GF products (n=5), or found it impossible to prepare and carry GF products when travelling (n=7).

I do my grocery from XXXX (Asian shop).. they don't have anything for gluten.. (CD2, 010, F, age 49), *"…no gluten products are available in our local store,* (CD2, 011, F, age 23), "..*Well sir it is restrictive when you go out, you cannot eat what other would like to eat…"* (CD2, 015, F, age 53),

Problem in following a GFD:

Patients in the non-adherent group (28) were asked specifically for problems faced in following a GFD; the multifactorial nature of the issue was evident. The bar chart below (Fig No 21) shows the reasons for poor adherence in the South Asian group (n=7).

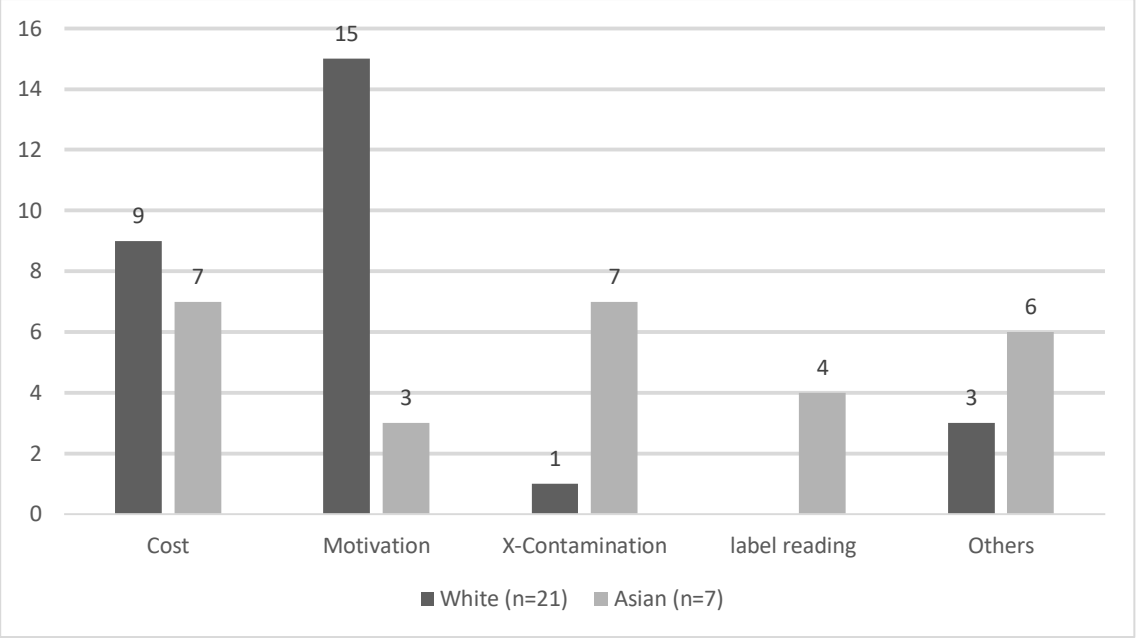

Figure 21: Problems in following a GFD reported by pts not adhering to a GF diet

GFD was reported by patients to be associated with high cost

"….gluten free product, it does not come cheap you see…"(CD02/002, F, Age 30), *"..it does not come cheap…* (CD02/004, F, Age 45), *"..very pleasant a diet, very cheap!! (being sarcastic)"..* (CD02/007, F, Age 49), and " *is restrictive in travelling.. dining out and not a cheap diet.."* (CD02/023, F, Age 42).

A GFD was considered restrictive by patients:

"well it is restrictive because what you can eat, where you eat and who you eat with is dependent on if you will eat gluten or not.. did I make it too complicated? (laughing) (CD02/004, F, Age 45), "*it is difficult and it takes away my control .. so a bit restrictive"* (CD02/024, F, Age 46), *"gluten (free) diet is … restrictive, one, and secondly it is restrictive in travelling.. dining out"* (CD02/023, F, Age 42), *"well you either have to go on this diet or socialise.. it is a restrictive diet.. one cannot follow it all the time, that is why it is not possible"* (CD02/019, F, Age 51), and "*well sir it is restrictive when you go out, you cannot eat what others would like to eat … that makes the choice of restaurants very limited for me.."* (CD02/015, F, Age 53).

Cross contamination is another issue which was a major intentional and unintentional barrier to GFD adherence. It was a non-modifiable factor to some extent as well. In the patients' words:

"…secondly the spices we bring from Pakistan, might well have contamination from the supplier or producer as we saw on the tele.." (CD02/017, F, Age 36) and "*again to avoid gluten…not to eat wheat, to avoid contamination while cooking but these are practical issues, easier said than done..* (CD02/018, F, Age 56).

Reward for GFD adherence:

All patients were given the option to select one out of five rewards, as an incentive for following a GFD. 12 patients selected monetary incentives, followed by the option of a holiday abroad. The breakdown of the results is given in the bar chart below (Fig No 22).

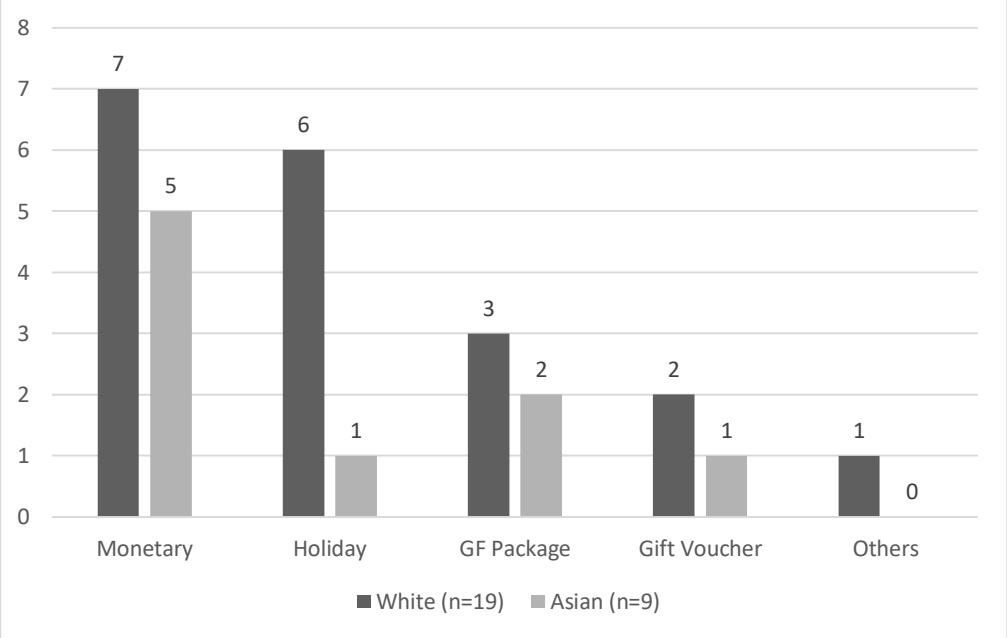

Figure 22: Patients' preference of reward for GFD adherence.

Miscellaneous themes:

There were several non-classifiable nodes (n=13) which were grouped under the miscellaneous category and are presented in the table below (Table No 36).

Table 36: Classification of Nodes in the main stem.

Node Type	Sources	References	Classification
Dietary Issues	16	20	Thematic, Analytic
Ready for GFD	29	77	Thematic, Analytic
Sarcasm about GFD	4	6	Thematic, Analytic
Specific issues	30	74	Descriptive
Religious issues	2	2	Descriptive
Food labelling GFD	2	4	Thematic, Analytic
Ideas about CD	33	111	Thematic, Analytic
Inadvertent gluten intake	1	1	Descriptive
Priorities GFD	28	29	Descriptive
Programme	28	35	Descriptive

Patients referred to religious issues (being vegetarian) in the context of a GFD:

"GP and these gluten free company what do you call them.. yes XXXX they only do English meals .. there are few vegetarian meal.. but you never know what they mix in it.. it is a matter of religion after all.." (CD02/012, F, Age 42), *"I cannot get my head around what is gluten free and what is not gluten free to be honest.. I ate rice for few weeks but then you cannot eat rice all your life, can you?* (CD02/013, F, Age 34) and *"well the labelling now shows the ingredients to a much greater extent than it used to do and usually it highlights the things that people are likely to be allergic to on the label itself.."* (CD02/032, M, Age 54)

Choice of Intervention:

A principal aim of the study was to ascertain the best mode of intervention based on patient views, to increase adherence to a GFD; approximately half of the interview time was spent probing this issue. Several nodes were grouped under this topic, as displayed in the table below (Table No 37).

Table 37: Classification of Nodes in the main stem.

Node Type	Sources	References	Classification
CD Day conference	32	289	Descriptive, Thematic
Planning to improve	18	19	Descriptive, Thematic, Analytic
Possible to be adherent	29	48	Descriptive, Analytic
Telephonic contact	29	64	Descriptive, Thematic, Analytic
Text messages	1	1	Descriptive, Thematic,
Website	6	10	Descriptive,
Ready to improve adherence	18	20	Descriptive, Thematic, Analytic
Emails and adherence	28	270	Descriptive, Thematic,
Face to face interview	1	1	Descriptive, Thematic, Analytic
Group interaction	0	0	Descriptive, Thematic, Analytic
Home visit	34	312	Descriptive,
Leaflets	10	16	Descriptive,
Method	29	30	Descriptive, Thematic, Analytic
Motivation	8	13	Descriptive, Thematic, Analytic

These options were grouped and weightage was assigned to different individual options based on participants' weightage, negative comments and thematic analysis; the idea is represented in the figure below (Fig No 23).

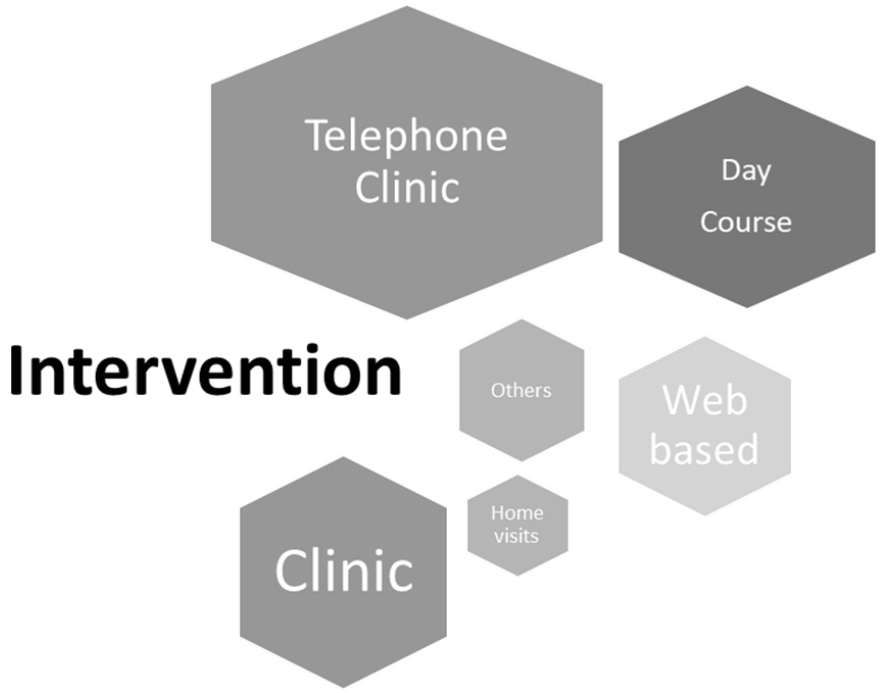

Figure 23: Intervention methods based on importance and frequency of nodes.

Standard clinic and dietitian appointment:

This theme was liked by 37 participants. All patients had seen a dietitian and clinician at some stage of their diagnosis. The theme was difficult to node under one heading, as it was partly shared by three main themes i.e. Hospital and CD, CD Clinics and Costs and CD. Although it was available as both clinician and dietitian appointments, the most favourable option was a combined clinic with dietitian and clinician and this was sourced from 12 sources and 12 references. Interestingly all adherent patients liked the concept and they had only positive comments about it. All patients liked the way dietitians explained CD and patient-related literature to them. Moreover, the way in which the clinician described the disease to them was well liked by all patients. In general terms, clinics were friendly (n=28), full of information (n=33) and useful (n=15), but a few patients found them difficult:

"Clinical appointments .. I have an issue with them, I have to take time off, arrange transport and a lot more…." (CD02/002, F, Age 30), "…*don't like the appointments.. and then arranging time off.. so possibly it is difficult for me..* (CD02/024, F, Age 46), and *I would love to see them again for a longer appointment you see.. if at all…*(CD02/001, F, Age 21),

Car parking was the main negative issue with regards to hospital appointments. Parking was considered unpredictable (n=23), difficult to get (n=20), expensive (36). Additionally, it was difficult to get into the car park and to exit the main barrier (n=7). Patients also highlighted negative aspects about the inability to pay through debit nor credit card (n=10) and that the parking payment machines would only accept coins and would not give change (n=11). Also, the parking payment machines were designed so that one had to pay for a pre-determined amount of time, which meant that there was potential for overpayment, as asserted by the patients:

"…think the hospital car park is a serious main issue .. costly and always eager to charge more.. that is the real issue …with clinical appointments. ..charges are on the mount and people pay a fine because they are late to collect their cars (CD02/015, F, Age 53), "…*many issues such as parking which is not cheap these days.. used to be reasonable a few years ago.. but now it is all about money you see..* (CD02/005, F, Age 74), and "..*Parking is another issue, very strange issue not sure how to describe it.."* (CD02/007, F, Age 49),

Other issues with clinics were: repeated cancellations and changes in time of attendance (n=10) and prolong waiting times; these were further aggravated by the over parking issues and related anxiety. Privacy in clinic was another issue raised by the participants (n=23):

"…you are seen by many people in the same clinical area where other people are sitting. They might know you.. privacy is non-existent in the NHS.. people shouting your name.. Mr this and that.. Mrs this and that.. honestly ..(sounding frustrated)" (CD02/003, M, Age 42), *Serious issues with the privacy.. no way I am going to discuss my personal problems there"* (CD02/014, F, Age 61), *I have heard people talking aloud and even in the clinical room you can hear what the other person is saying, no privacy at all. How can you bring up emotional subjects when people are listening to you outside?* (CD02/009, F, Age 65).

Telephonic clinic:

A telephonic clinic idea was liked by both adherent and non-adherent participants. This was based on the seriousness of individual interview responses and node frequency. It had 29 associated nodes and

64 references and was liked by a clear majority of the participants (n=33); this was then sub divided into four sub nodes as detailed in the table below (Table No 38).

Table 38: Classification of Nodes and telephonic clinic.

Node Type	Sources	References	Classification
Telephonic clinic	10	19	Descriptive, Thematic, Analytic
Telephone pros and cons	37	65	Descriptive, Thematic, Analytic
Telephonic contact method	33	46	Descriptive, Thematic, Analytic
Telephonic interaction	31	271	Descriptive, Thematic, Analytic

Telephonic interaction was considered easy (n=33), flexible (n=29) and convenient (n=19) for the patients. Theme analysis showed that patients approved of it as a practical intervention based on their experience of using the telephone in both personal and professional life. It was considered important for privacy (n=27) and ease of communication (n=18). In addition to that, the telephonic clinic gave control to the patients to stop the conversation when they wanted to (n=20). This theme was further explored and, based on patients' experience (n=8), they could hang up without giving any specific reason to the interviewer.

The themes were analysed for pros and cons of a telephonic interview. A clear majority of participants considered this method friendly (n=25), convenient and deliverable in the ease of their home environment. This has the added advantage of privacy and being cost effective to the patients (n=28). Furthermore, this was eco-friendly (n=27) as it avoids driving to hospital or another face to face contact, thus avoiding adding to the carbon footprint. .

Telephonic teaching in conjunction with a supplement leaflet was favoured by 31 patients. The figure below shows the theme as perceived by the participants in the study. There were however concerns such as lack of face-to-face contact for the participants, which may lead to an uncomfortable situation, as body language may not be read by either the health care professional or the participant. The telephonic clinic was predominantly considered acceptable and practical to the patients based on ease, cost, flexibility and privacy and this is represented in the figure below (Fig No 24).

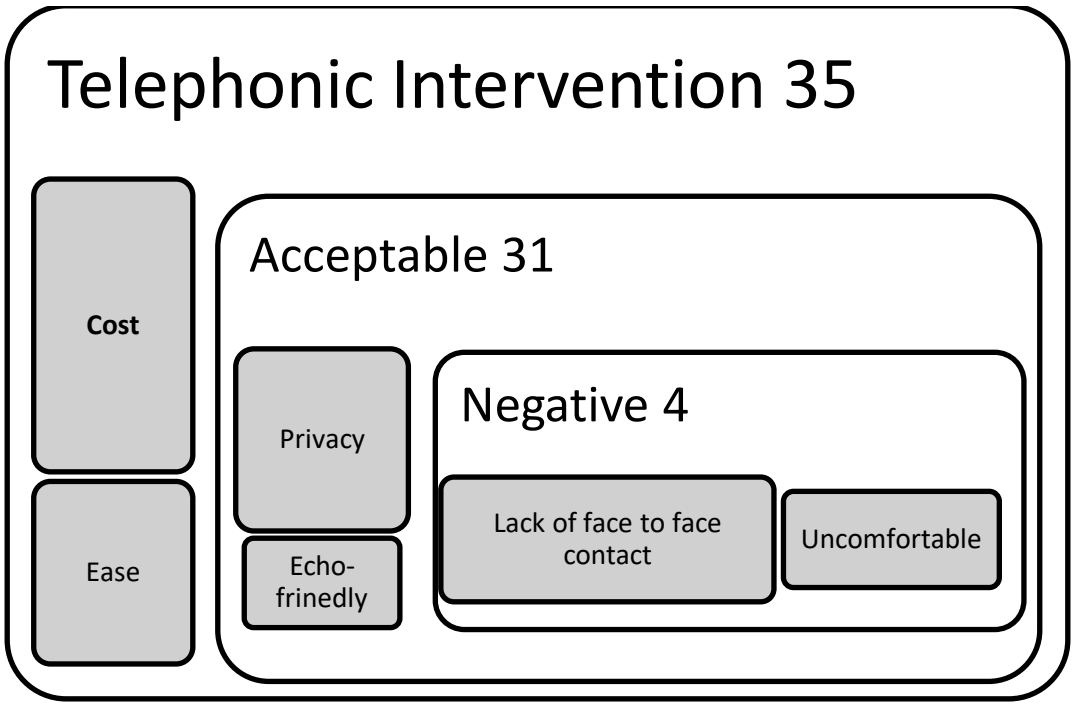

Figure 24: Telephonic clinic pros and cons.

CD day conference:

A CD day conference was featured in 289 references and from 32 sources. A clear majority of patients (n=24) liked the idea and it was opposed by six patients; the remaining patients had a neutral opinion about it. The breakdown of sub themes is given in the table below (table No 39).

Table 39: Classification of Nodes and CD day conference.

Node Type	Sources	References	Classification
Information lecture	6	8	Descriptive, Thematic, Analytic
Course	8	9	Descriptive, Thematic, Analytic
Negative comments	1	1	Descriptive, Thematic, Analytic
Positive comments	1	1	Descriptive, Thematic, Analytic
CD talk	37	126	Descriptive, Thematic, Analytic

The perceived usefulness of a conference was related to the focused nature of the educational material on CD (n=20). Additionally, it was thought that the topics would be diverse, with a multiplicity of

presenters (n=4), providing detailed views from experts in the field. Moreover, group activity was valued highly among several patients (n=18), mainly Caucasian, due to the advantages of socialising (n=10) and associated group support (n=10). Thematic analysis showed that lecture based talks were also acceptable to patients (n=6), as they found this traditional teaching method equally effective. Lectures were thought to be an effective source of background information (Nodes=6, References=8) and these ideas could subsequently be developed through private study.

Several participants (n=9) thought it was a good idea if the lectures were part of a course over a few weeks (Nodes=8, References=9). Three participants thought that lectures were passive activity and there was only a limited role for lecture based education in changing attitudes and behaviour; this was partly related to an inability to attend such events, as suggested by patients:

"…not sure if that is going to be useful though .. but will give it a go" (CD02/008, M, Age 65), *"…possibly difficult for me at this stage, I am too busy to attend group discussions.."* (CD02/002, F, Age 30), *"…no issue at all… but it might not be possible to come to the course.. depends.."* (CD19/002, F, Age 51), *"….that will be good, and I will; agree with this.. not sure I will be able to come for the whole day.. arranging a day off for a coeliac disease type day.. may not be possible.. I have a manager you see."* (CD02/001, F, Age 21).

The figure below shows the theme as perceived by the participants (Fig No 25).

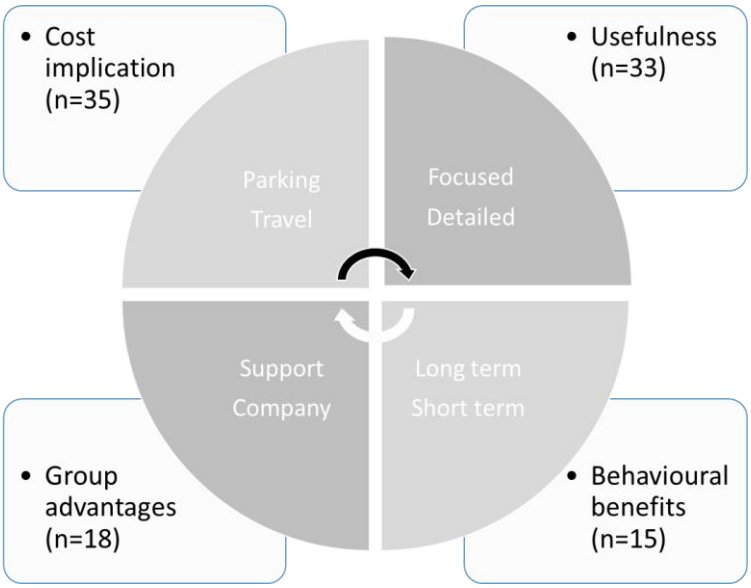

Figure 25: Coeliac disease day and related themes.

Cost was an issue for a majority of patients (n=33) in particular travel (n=17) and parking (n=12) related costs; this was one of the deterring factors as suggested by patients:

"…and then parking is a very difficult issue you see.." (CD02/001, F, Age 21), *"but car parking, waiting for the appointment is an issue"* (CD02/017, F, Age 36), *"many issues such as parking which is not cheap these days.. used to be reasonable few years ago"* (CD02/005, F, Age 74), *"parking in the hospital you see that is another issue..* (CD02/002, F, Age 30), *and car parking in the hospital is also an issue.. ..* (CD02/025, F, Age 19) and *" …honestly .. and car parking.. don't even go there"* (CD02/003, F, Age 42).

Other deterring factors were: privacy related issues (n=7), clashes with job commitments (n=13), and availability of time for a day's conference (n=4). It is thus inferred that lecture based teaching was well liked by participants but was at a cost to them and considerable time commitment.

Web based teaching:

This was sourced from 6 sources and 10 references. Web based teaching received 13 "yes" comments from participants, mainly females (n=11). All of those who approved this methodology insisted on related video links being included, as "dry slides" were considered boring. The table below shows the breakdown of sub nodes for this intervention (Table No 40).

Table 40: Classification of Nodes and web based teaching.

Node Type	Sources	References	Classification
Computer based teaching	19	20	Descriptive
Internet based programme	29	40	Descriptive, Thematic
Negative comments	3	5	Descriptive, Thematic, Analytic
Role of social media	2	2	Descriptive, Thematic, Analytic
Web based approach	20	26	Descriptive, Thematic, Analytic

There were mixed views from the patients about web based teaching and in the patients' words:

"hmmm.. may be a good idea.. maybe.. internet.." (CD02/022, F, Age 50), *"not sure.. not a very attractive idea.. for me at least internet" (CD02/023, F, Age 42), This will work for me yes especially with videos in it.. Explaining the concepts"* (CD02/002, F, Age 30), and *"I think this will engage me but think of other people who might not be internet learned for a variety of reasons. Not sure one can generalize this idea .. "* (CD02/005, F, Age 74).

Theme analysis revealed that such a methodology was practical only if patients had the chance to interact with an instructor. The main issues attached to web based teaching were: computer literacy, dependence on technology, internet access and attached costs to the patients. The figure below shows the themes and patient views about web based teaching (Fig No 26).

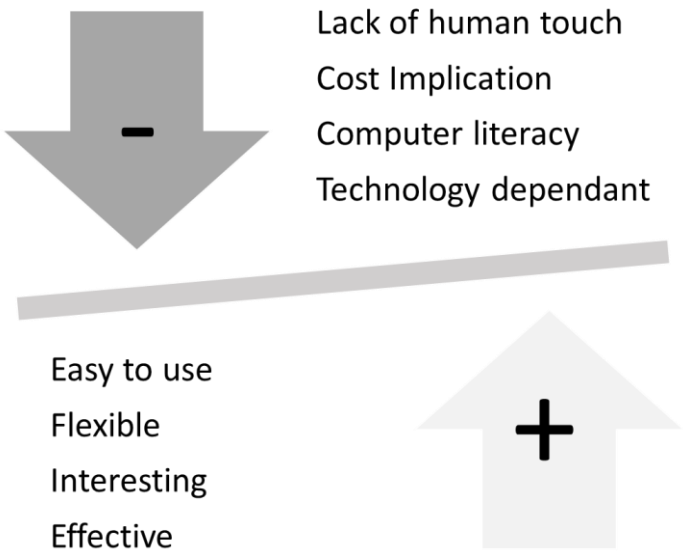

Figure 26: Web based teaching and theme analysis.

Home Visits:

This was sourced from 34 sources and 312 references. 35 patients opposed home visits as a possible intervention, based on a variety of issues including: being intrusive (n=8), breach of private life (n=9), uncomfortable (n=10) and difficult to arrange (n=11).

"..home might be difficult.." (CD02/024, F, Age 46), *"..not a feasible option.."* (CD02/003, M, Age 42), *At home? No.. I think it is difficult.. not sure about that."* (CD02/002, M, Age 42), *"See .. well .. not sure.. I think no…"* (CD02/020, F, Age 29) *and "home.. no way.. do you think it is a good idea to go to .. well (laughing)* (CD02/028, F, Age 30).

Since this was a sensitive issue, and not liked by the majority of participants it was not explored in further detail.

Other themes and adjuvant measures:

Compact discs, DVDs or books were only favoured by two of the participants. A YouTube® link was favoured (n=20), but only in relation to web based teaching. Intervention through Skype® was favoured by nine patients and group calls were rejected by 35 patients. Although email was accepted by 25 patients but text messages were not favoured (n=28). Email related teaching was not considered productive by 31 participants.

"I get so many email and .. Well I might not get through them you see.." (CD02/01, F, Age 21). "*Emails have their own issues.. I mean spam etc..* (CD02/02, F, Age 31). "*Emails, hmm.. good.. will give it a try, not sure it will affect me a lot***..** (CD02/04, M, Age 45).

The figure below summarises the main issues in Miscellaneous or adjuvant themes (Fig No 27).

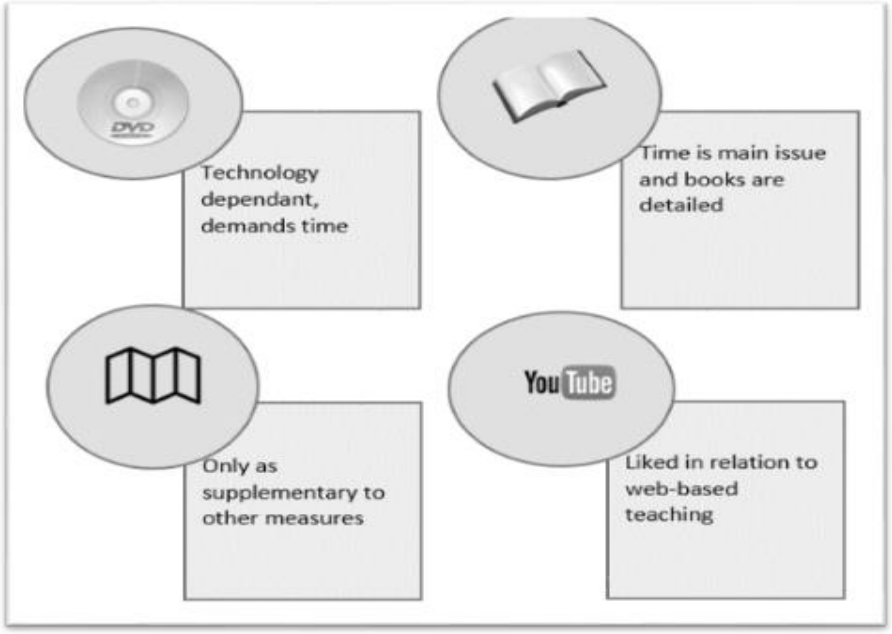

Figure 27: Patients' views on printed and web based material.

Comparative analysis:

All participants were asked to assign a number from 1 to 10 to each mode of intervention against certain parameters. CD day conference and telephonic clinic achieved the highest overall value (8), followed by standard clinic. Telephonic clinic, home visit and Skype were the least expensive options. The trend was similar for both adherent (n=9) as well as non-adherent patents (n=28). The results of the comparative analysis for cost and usefulness of the methods of interventions are given in the bar chart below (Fig No 28).

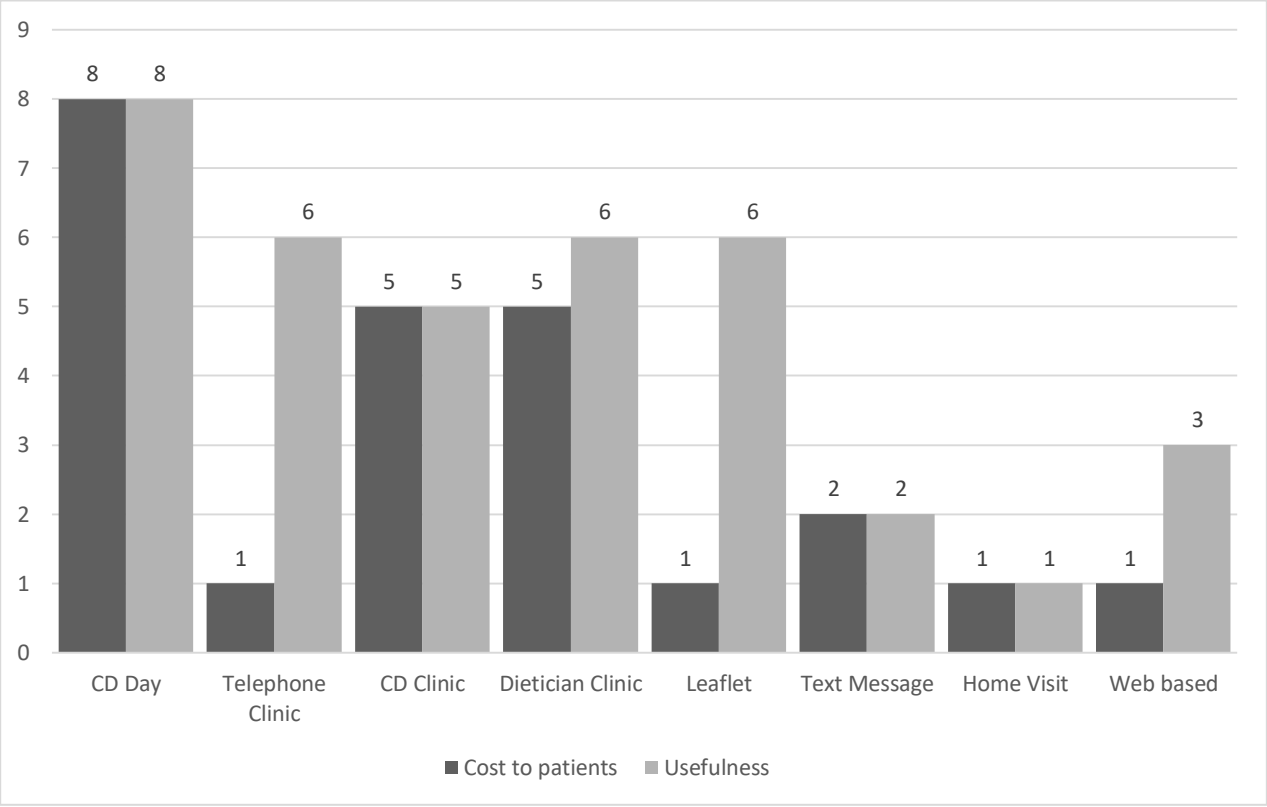

Figure 28: Mean values form Likert scale (n=37). Comparative analysis of all available methods of intervention. High cost is a detriment to patient and vice versa. High usefulness is a benefit and promotes the choice of methodology. Y Axis shows Likert scale.

Based on the above bar chart, as suggested by the participants, it can be inferred that the telephonic clinic is considered the most cost effective method and convenient for the patient as it has low cost attached to it but has relatively high usefulness for the patients.

SECTION V

Comparison of knowledge, adherence to a gluten free diet and difficulties faced by Asians and Caucasians in relation to coeliac disease

There were 21 White Caucasians (75%) and 7 South Asians (25%) interviewed who were not adhering to the GF diet. All South Asians were born outside the UK but has spent more than 10 years in the UK. Fifteen (53.6%) patients were members of the Coeliac Society of the UK. The ages ranged from 19 to 74 years (M = 42.8, SD = 14.8). The table below shows their demographics (Table No 41).

Table 41: Characteristics of population according to gender

		Ethnicity		
Variables	**Total**	**White Caucasian**	**South Asian**	***P* Value**
	n=28	21 (75 %)	7 (25%)	
Mean Age ± SD	42.8± 14.8	44.8 ± 15.9	37 ± 9.3	.23*
Gender				1.0**
Male	4 (14.3%)	3(10.7%)	1 (3.6%)	
Female	24 (85.7%)	18 (64.3%)	6 (21.4%)	

***Independent sample T test, **Chi Square test**

The sample was mainly White Caucasian and the dominant gender was female, but there was no significant difference between the ages of the White Caucasians (M=44.8, SD=15.9) and South Asians (M=37, SD=9.3), Conditions; t (26) =-1.21, p=.23. Likewise there was no significant difference between the genders, $\chi 2$ (1, n=28) =.00, p= 1, phi = .00 (Appendices 4.2Ea-c). The patient CDAT scores ranged from 10 to 29 (M = 20, SD = 5.4). CDAT scores for White Caucasians ranged from 11 to 28 (M = 19.2, SD = 4.8) similarly, CDAT scores for the South Asian population ranged from 10 to 29 (M = 22.2, SD = 6.7) and there was no significant difference between these scores (Appendix 4.2Ed)

Knowledge about CD:

Knowledge about CD was classified in 10 nodes and it was derived from 11 references and multiple field notes (n=17). All participants commented about this issue. There were three sub nodes which were

further classified into 15 nodes. Sub nodes were further classified into daughter nodes. Theme analysis was related to other nodes such as: complications of CD, miscellaneous, symptoms of CD and food label reading. The main theme was source of knowledge, which was mainly from dietitians and patients showed satisfaction with the information provided, as shown in the table below (Table No 42).

Table 42: Classification of Nodes in the main stem.

Node Type	Sources	References	Classification
1 Knowledge about CD	10	11	Descriptive
1.1 Information CD	37	368	Descriptive, Thematic, Analytic
1.11 Coeliac	13	14	Descriptive, Thematic, Analytic
1.111 CD health	3	3	Descriptive, Thematic
1.12 Coeliac day to day	3	3	Descriptive, Thematic, Analytic
2 Knowledge other	6	20	Descriptive, Thematic, Analytic
1.1 CD Related	5	6	Descriptive, Thematic, Analytic
1.2 Bone health	13	29	Descriptive, Thematic, Analytic
1.3 CD Social	1	1	Descriptive, Thematic, Analytic
1.4 CD Complication a	4	9	Descriptive, Thematic, Analytic
1.5 CD Complication b	1	1	Descriptive, Thematic
1.6 CD and GUT	9	17	Descriptive, Thematic, Analytic
1.7 CD Causes	1	1	Descriptive, Thematic, Analytic
1.71 Complication	1	1	Descriptive
1.72 Symptoms	2	3	Descriptive
1.8 CD understanding	27	63	Descriptive, Thematic, Analytic
1.9 GFD usefulness	1	1	Descriptive, Thematic, Analytic
1.10 Wheat	22	17	Descriptive, Thematic, Analytic
3 Source of information	37	126	Descriptive, Thematic, Analytic
3.1 Dietitian and clinician	3	3	Descriptive, Thematic
3.2 Internet	4	5	Descriptive, Thematic
3.3 Others	1	1	Descriptive, Thematic

The majority of patients (n=26) correctly linked wheat to CD, but the information was patchy about the exact relationship with wheat. Four patients thought that CD would cause cancer at some stage in their lives, while others (n=11) thought that consuming a small amount of wheat was not harmful. Additionally, knowledge about a GFD was not uniform and 13 patients thought a GFD was for weight loss in CD. Similarly, another six patients thought a GFD meant only avoiding wheat. Interestingly, three Asians patients thought only wheat in Chapattis was harmful in CD. Following on from this, different areas were explored in a quantitative manner and the table below shows the results of a series of questions that patients were asked in order to explore these aspects (Table No 43)

Table 43: Comparison of White Caucasians and South Asians in following a gluten free diet

	Total (n=28)			White Caucasian (n=21, 75%)			South Asians (N=7, 25%)			
Variables	M±SD	Mdn (IQR)	Min-Max	M±SD	Mdn (IQR)	Min-Max	M±SD	Mdn (IQR)	Min-Max	P
Age	42.8± 14.8	42 (30-50)	19-74	44.8 ± 15.9	45 (31-58)	19-74	37 ± 9.3	36 (29-46)	23-49	.23*
CDAT Score	20.04±5.4	19 (15-26)	10-19	19.2±4.8	19 (15-230	11-28	22.2±6.7	25 (18-28)	10-29	.21*
Sufficiency of information Gluten	70.3±26.4	80 (60-90)	0-100	74.7±20.4	80 (70-90)	30-100	57.1±38.6	60 (10-90)	0-100	.34**
Sufficiency of information GFD	68.2±23.7	80 (50-80)	0-100	72.8±19.2	80 (65-80)	30-100	57.1±33.0	50 (40-80)	0-100	.29**
Confidence about GFD	68.2±21.2	70 (60-80)	10-100	71.9±16.6	70 (65-80)	30-100	57.1±30.3	70 (30-80)	10-90	.43**
Eating home cooked meal per week	72.5±18.5	80 (60-87)	30-100	66.1±16.8	70 (55-80)	30-90	91.4±8.9	90 (80-100)	80-100	**.00***
Order cooked meal / eat out per week	38.1±23.3	40 (30-50)	0-90	44.5±21.6	40 (30-57)	10-90	20.0±19.1	30 (0-40)	0-40	**<0.01***
Confidence in person preparing meal	39.5±26.5	40 (10-50)	0-90	45.2±23.6	50 (3-60)	10-90	12.5±25.0	0 (0-37.5)	0-50	**.02***
Difficulty following GFD eating out	84.8±21	90 (90-100)	0-100	81.9±22.7	90 (70-100)	0-100	95.0±8.3	100 (87-100)	80-100	.12**
Difficulty following GFD in friend's house	93.9±8.7	100 (90-100)	70-100	91.9±9.2	90 (85-100)	70-100	100.0± --	100 (100-100)	100-100	**.04****
Difficulty following GFD travelling	90.3±11.0	90 (80-100)	70-100	88.1±11.23	90 (80-100)	70-100	97.1±7.5	100 (100-100)	80-100	**.04****
Sufficiency of GFD on prescription	45.1±18.0	50 (30-60)	10-70	50.0±15.2	50 (32-60)	20-70	31.4±19.5	30 (10-50)	10-60	**.03****
Difficulty buying GFD	78.1±21.1	80 (70-90)	0-100	80±15.2	80 (70-90)	40-100	72.8±34.0	90 (70-90)	0-100	.97**
Availability of GFD in store	70.3±44.0	100 (10-100)	0-100	88.5±28.3	100 (90-100)	0-100	15.7±37.3	0 (0-10)	0-100	**<0.01****
Problem with taste of GFD	30.3±18.7	30 (20-40)	0-80	27.6±14.8	30 (20-40)	0-50	38.5±27.3	30 (10-70)	10-80	.18*
Improvement on GFD	34.2±24.4	30 (20-47)	0-90	28.1±19.3	30 (10-400	0-70	52.86±29.8	40 (30-90)	20-90	**.01***
Symptoms after gluten ingestion	31.07±20.0	30 (12-40)	0-90	24.7±14.0	30 (10-400	0-50	50±24.4	50 (30-80)	20-80	**.02****

*Independent sample *t* test, **MWU test

The table above shows that there exists significant differences in relation to eating food at home and ordering precooked meals. In addition to that, there is also a significant difference in confidence in the person who serves the meal (in restaurants), difficulty following a GFD in a friend's house, sufficiency of GFD on prescription, availability of GFD in (local) stores, improvement on GFD and post gluten symptoms (Appendices 4.2F a-f)

Node analysis suggested that this area was directly or indirectly affected by several nodes i.e. knowledge about CD, eating out, restaurant, shopping and CD, sources of knowledge about CD and hospital and dietitian appointment. There was lack of understanding in terms of long term beneficial effect of GFD on health. Additionally, unavailability of GFD in local stores (Asian) was another issue which may affect confidence of the patients in adherence to a GFD.

This area could not be explore in depth and will need in depth interview based research but It is may be inferred that, although the confidence level was reasonable among patients and there was no difference between the ethnicities. In terms of node analysis, this area was widespread and was covered by: cooking at home, restaurant, travelling, dining at friends' and costs related to a GFD. The breakdown of the relevant nodes is given in the table below (Table No 44).

Table 44: Classification of Nodes in the main stem.

Node Type	Sources	References	Classification
1 Problems following GFD	2	3	Descriptive
1.1 Problems with GFD	23	34	Descriptive, Thematic, Analytic
1.2 Symptoms post GFD	3	4	Descriptive, Thematic, Analytic
2 Restaurant and CD	5	7	Descriptive, Thematic, Analytic
2.1 Restaurant	8	11	Descriptive, Thematic, Analytic
2.2 Restaurant Knowledge	1	1	Descriptive, Thematic, Analytic
2.3 Restaurant Issues	6	8	Descriptive, Thematic, Analytic
3 Prescription and GFD	8	9	Descriptive
3.1 Negative	4	4	Descriptive, Thematic, Analytic
4 GFD	37	37	Descriptive
4.1 GFD not available	6	7	Descriptive, Thematic, Analytic
4.2 GFD restrictive	10	14	Descriptive, Thematic, Analytic
4.3 GFD Supermarket	6	8	Descriptive, Thematic
4.4 GFD Taste and issues	7	8	Descriptive, Thematic, Analytic
4.4 GFD difficulties			Descriptive, Thematic, Analytic
5 Misc. Issues			
5.1 Inadvertent Gluten intake	1	1	Descriptive, Thematic, Analytic
5.2 GFD priority	28	29	Descriptive, Thematic
5.3 Others	30	75	Descriptive, Thematic

Several problems were encountered in following a GFD and there was a distinct difference in themes when comparing the two ethnicities. The majority of Asians (90%) cooked at home and for the whole family, which posed a special issue of demarcation of a GF area in the kitchen. There was frequent cross contamination (n=6) from family members and guests when invited. This was linked to associated frustration and anxiety amongst Asian patients (n=3).

"I have to cook for the family and not possible to avoid complete separation from gluten world.. I do knead dough myself..(CD02/011, F, Age 23), *"I have the responsibility to cook for the whole family and we eat wheat all the time as bread.. difficult to control oneself.."* (CD02/016, F, Age 46) and

"….causes are slightly beyond my control.. none of my family understands the importance of gluten free diet.. and I cannot make separate food for myself…I have to eat what all eat.." (CD02/017, F, Age 36),

Those White Caucasians who did not cook at home (n=14) tended to have concerns about whether their ordered meal was gluten free or not. Theme analysis showed that this area was difficult to probe as it was multifactorial (n=26).

Buying Gluten Free products (GFP) again posed two specific issues: cost and availability. Cost related issues have been explained above. Considering the availability, South Asian participants reported virtually no Asian supermarkets had any idea about GFP and they did not sell any GFP, whereas all major western supermarkets e.g. TESCO, Sainsbury and ASDA had clearly demarcated GF areas. This led to difficulty in obtaining GFP for the Asian patients in their local area and they resorted to the main supermarket, which was an inconveniences and source of poor quality of life. Theme analysis again showed that this area was difficult to probe as it was multifactorial (n=26). Patients' comments included:
:

"I do my grocery from XXXX (Asian Shop).. they don't have anything for gluten like Tesco has and that is too expensive" (CD02/010, F, Age 49), *"…no gluten products are available in our local store…"* (CD02/011, F, Age 23), and "….*issue is non availability of gluten free products in local shops and we have to go to XXX or …..since I don't drive I am dependent on my son to bring that for me"* (CD02/017, F, Age 36) and *"…we have issues as it is difficult to find local stores who sell gluten free products.."* (CD02/013, F, Age 34).

It was particularly difficult for frequent restaurant-eaters to find a reliable restaurant where GF food was served, although it was felt by patients (n=4) that awareness about a GFD was increasing among restaurants. This clearly had an impact on quality of life (n=10). Since the majority of the South Asians (n=6) were not eating outside on frequent basis, is likely to only have a minor (if any) role in their quality of life.

These concepts were then assessed in a quantitative manner. Firstly the patients were asked about the number of times they ate a cooked meal at home. Ninety two percent of Asians eat a cooked meal at home, whereas only 65% of Caucasians ate a home cooked meal every day. Similarly, when they were asked about the number of times they ordered a meal out, only 15% of Asians said yes, in contrast to

46% of Caucasians. When asked how confident they were that the person serving the meal was aware of their GFD requirements, only 15% of the Asians showed confidence; in contrast 44% of Caucasians showed confidence in the restaurant staff (Table No 27).

There was a significant difference between White Caucasians (Mdn = 70, IQR = 55-80) and South Asians (Mdn =90, IQR = 80-100) in relation to eating at home, U = 12, z = -3.31, *p* = <0.01, r = -.63. Similarly there was also a significant difference between White Caucasians (Mdn = 70, IQR = 55-80) and South Asians (Mdn =90, IQR = 80-100) in relation to eating out, U = 28, z = -2.3, *p* = 0.01, r = -.1. The results are displayed in the figure below (Fig No 29) (Appendices 4.2 Fa-c).

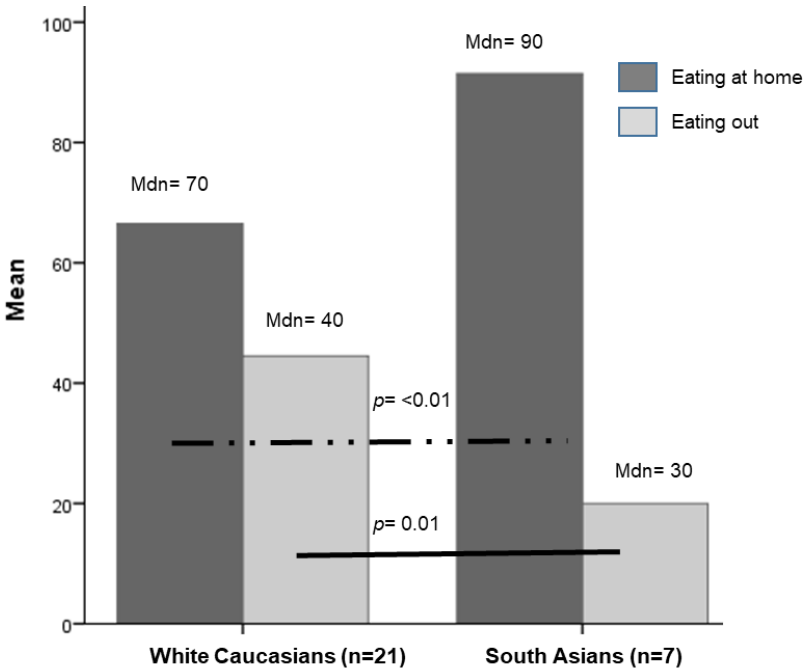

Figure 29: Significance of dinning habits in relation to White (Mdn = 70, IQR = 55-80) and Asian (Mdn =90, IQR = 80-100) ethnicity. (MW U test).

The results suggests that the White Caucasian population tend to eat out more when compared to the South Asians; conversely South Asians tend to eat more home cooked food than their White Caucasian counterparts. Similarly, in relation to the issue of preparing GF meals at home, 53% of patients had issues, but this was not significantly different when analysed according to the ethnicity; $\chi 2$ (1, n=28) = 1.19, p=.27, phi = -.20.

Next, the level of difficulty in following a GFD in three special situations was assessed: eating out, dining at a friend's house and travelling. A clear majority of patients (around 90%) had issues in these special situations. The results are displayed in the bar chart below (Fig No 30).

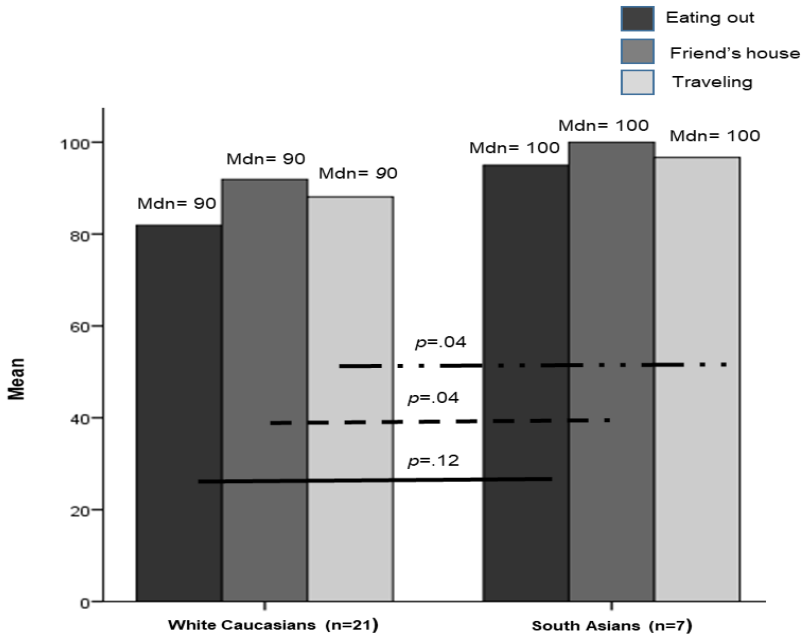

Figure 30: Comparing ethnicities and special situations in relation to a GFD (MW U test)

It is clear that, although there was no significant difference in the difficulties faced when eating out (between the ethnicities), there were a significance differences when eating at a friend's house: Asians (Mdn 100, n = 7) and Caucasians (Mdn=90 , n = 21), U = 36, z = -2.33, p = .04, r = -.44 or travelling: Asians (Mdn 100, n = 7) and Caucasians (Mdn=90, n = 21), U = 36, z = -2.09, p = .04, r = -.40.This suggests that South Asians had significantly more issues in both travelling and dining at a friend's house. (Appendices 4.2G a-f)

Both groups were then asked to comment on certain statements in relation a GFD. The participants commented on these statements as "yes" or "no" and the results are displayed in the table below (Table No 45)

Table 45: Ethnic differences in relation a GFD

Statements	Total		White Caucasian		South Asian		
Do you/ do you have /have you/ what is…..	**Yes (%)**	**No (%)**	**Yes (%)**	**No (%)**	**Yes (%)**	**No (%)**	**P**
Issues with preparing GF meal?	15 (54)	13 (46)	10 (36)	11(39)	5(18)	2 (7)	.27***
Read food labels	24 (86)	4 (14)	20 (71)	1 (4)	4 (14)	3 (11)	**.01*** **
Understand food labels	21 (75)	7 (25)	20 (71)	1 (4)	1 (4)	6 (21)	**<0.01*** **
Know about gluten in cosmetics etc?	3 (11)	25 (89)	2 (7)	19 (68)	1 (4)	6 (21)	.72***
Heard anything negative about GFD	13 (46)	15 (54)	11 (39)	10 (36)	2 (7)	5 (18)	.27***
Membership of Coeliac UK	13 (46)	15 (54)	12 (43)	9 (32)	1 (4)	6 (21)	**.04*** **

***Chi square

Table above shows that there exists significant differences between both ethnicities in relation to reading and understanding food labels and membership of coeliac UK. (Appendices 4.2G a-f)

Sufficiency of information and confidence level about a GFD:

Sufficiency of information about gluten containing food (GCF) ranged from 0 to 100 (Mdn = 80.3, SIQR=60-90) and was non-normally distributed (p=0.00), with skewness of -1.33 (SE = .44) and kurtosis of 1.06 (SE = .85). Sufficiency of information about a GFD ranged from 0 to 100 (Mdn = 80, IQR = 50-80) and was non-normally distributed (p=0.00), with skewness of -1.1 (SE = .44) and kurtosis of 1.22 (SE = .85) but there was no significant difference on ethnic analysis. The results are displayed in the figure below (Fig No 31)

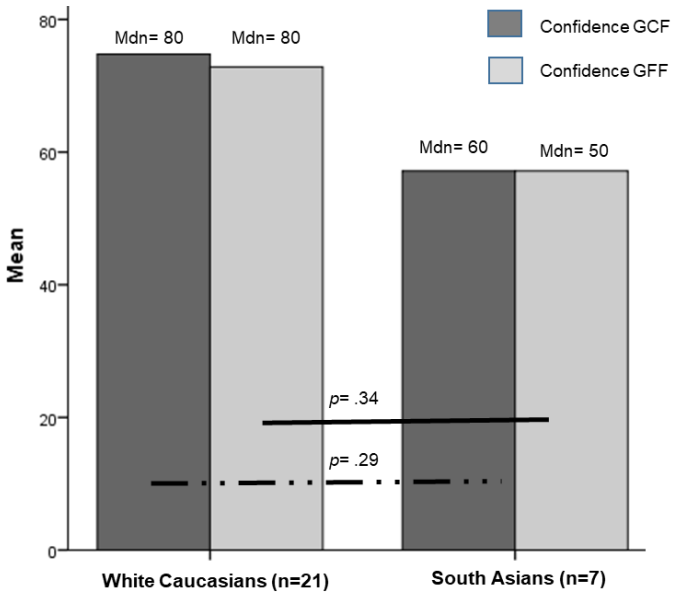

Figure 31: Comparing ethnicities and special situations in relation to a GFD (MW U test)

The confidence level post counselling about a GFD and related education ranged from 10 to 100 (M = 68.2, SD = 21.2) and was non-normally distributed (p=0.03), with skewness of -.99 (SE = .44) and kurtosis of 1.03 (SE = .85). When analysed according to ethnicity there was no significant difference between South Asians (Mdn 70, n = 7) and White Caucasians (Mdn 70, n = 21), U = 58.5, z = -.81, p = .41. r = -.15. Similarly, in relation to confidence they had in pre-ordered or restaurant food being gluten free, only 23 participants answered this question and only 15% of the South Asians showed confidence in restaurant staff, in contrast to 44% of White Caucasians. This result was significant (p=.02), suggesting that South Asians had less confidence in restaurant staff when compared with White Caucasians. (Appendices 4.2G a-f)

Finally, questions were posed to evaluate the level of help received from GPs and 27 patients replied to these questions. Theme analysis suggested that GPs were under prescribing GFP as suggested by the patients:

"….marginal if any help from GP, used to be quite good though" (CD02/005, F, Age 74), *" (GP Helps) to some extent though"* (CD02/008, M, Age 65),*"….marginal help and they give me English food like pizza.. pasta.. we don't eat that.."* (CD02/011, F, Age 23) and "…nothing.. no help.." (CD02/016, F, Age 46)

The MWU test was used to compare sufficiency of GFP from the GP and it showed significant difference between Asians (Mdn 30, n = 7) and Caucasians (Mdn 50, n = 20), U = 31.5, z = -2.17, p = .03, r = -.41. This suggests that South Asians were getting comparatively fewer GFP on prescription from their GPs

Availability of GFP was an issue in local Asian stores and not in supermarkets, as suggested by all patients. Scores ranged from 0 to 100 (M = 70, SD = 44) and was non-normally distributed (p=0.00), with skewness of -.97 (SE = .44) and kurtosis of -1.06 (SE = .85). A MWU test indicated there was a significant difference between the availability of GFP in local stores reported by Asians (Mdn 0, n = 7) and Caucasians (Mdn 100, n = 21), U = 17, z = -3.3, p = .00, r = -.62. Moreover, there was a significant difference between White Caucasians (M = 80, SD = 15.2) and South Asians (M =73, SD = 34.0) conditions; t (25) =.76, p = .45 in terms of difficulty buying GFP but there was no significant difference in the difficulty experienced when buying GFP, White Caucasians (M = 80, SD = 15.2) and South Asians (M =73, SD = 34.0) conditions; t (25) =.76, p = .45. These results suggests that it was significantly more difficult for South Asians to obtain GFP from local Asian stores, but that there was no difference in buying power of GFP between both ethnicities. (Appendices 4.2F a-f)

Miscellaneous issues in relation to a GFD:

Several miscellaneous issues were also explored, among them food labelling. The results showed that 24 patients (85.7%) read labels before buying food and 71% of White Caucasians would read food labels in comparison to 14.3% of South Asians; a chi-square for independence showed a significant difference between ethnicity and reading of food labels, $\chi 2$ (1, n=28) = 6.22, p=.01, phi = -.47.. Similarly, the comprehension of food labels was acknowledged by 21 (75%) of the participants, predominantly in White Caucasians (75%) as compared to South Asians (3.6%); a chi-square for independence showed a significant difference between the ethnicities in relation to the comprehension of food labelling; $\chi 2$ (1, n=28) = 18.3, p=.00, phi = -.81. This means that South Asians were significantly less often reading the food labels and had significantly less comprehension of them..

Gluten is found in minute quantities in cosmetics etc. and the results showed that only 3 (11%) of the participants knew about that; among the non-informed there was no significant difference based on ethnicity $\chi 2$ (1, n=28) = .124, p=.72, phi = .06. A question was also posed about negative press in relation to a GFD.13 (46%) had heard about this, mostly on the internet (39%) and from other sources (32%)

i.e. social media, friends and relatives, but there was no significant difference between the ethnicities: χ2 (1, n=28) = 1.83, p=.40, phi = .25. Similarly, the results showed that the taste of GFP was an issue ranging from 0 (no issue at all) to 90 (severely disliked), but no significant difference was found between White Caucasians (M 27.6=, SD = 14.8) and South Asians (M =38.5, SD = 27.3) conditions; t (26) =-.135, p = .18. (Appendices 4.2G a-f)

In relation to a GFD, information about improvement on the diet was also explored and it ranged from 20 to 90 (M=52.8, SD=29.8); this was significantly different between White Caucasians (M 28.1=, SD = 19.3) and South Asians (M =52.8, SD = 29.8) conditions; t (26) =-2.55, p = .01. This means that South Asians drew more symptomatic benefits from a GFD. Equally, when they were asked if they developed symptoms after the ingestion of gluten, a significant difference was found between Asians (Mdn 50, n = 7) and Caucasians (Mdn 30, n = 21), U = 30, z = -2.3, p = .02, r = -.44. This means that South Asians experience significantly more symptoms after ingestion of a gluten containing food items. Finally, membership of the advocacy group (Coeliac Society UK) was also explored and 13 (46.4%) were current members of the Coeliac Society. Among them, 12 (43%) were White Caucasians and 1 was South Asian. This difference was significant; χ2 (1, n=28) = 3.87, p=.04, phi = .25.

SECTION VI

Discussion:

A clear majority of the patients in this semi-structured, mixed methods interview opted for telephonic clinic as an option for intervention to increase adherence to GFD in CD. Additionally, leaflet was considered an adjuvant of telephonic clinic but not a standalone method of intervention. The interview was well received by the participants and this trend has previously been observed in relation to telephonic interviews (Stone & Rowles, 2007). However, no claims are made to assert the definitive superior role of telephonic interviews in extracting qualitative data and it is accepted that this area is under-researched, as suggested by Cachia and Millward (2011).

This may be a selection bias caused by participants' willingness to be interviewed and it may be possible that only those participants who were motivated to change responded to the interview invitation. Furthermore, there exists a wide variation in behaviour among patients in regards to adherence to medicinal recommendations (DiMatteo, 2004). Ideally the study would also include those who are not motivated and although research has indicated ways to increase participation in surveys (Edwards et al., 2009), there is no credible research to show how participation in telephonic interviews may be increased in a completely unbiased way.

It has previously been observed, in a systematic review, that patient involvement may contribute to a range of healthcare strategies (Crawford et al., 2002) and a telephonic interactive voice response system has recently been used in relation to paediatric CD (Lionetti et al., 2017) but our study is a seminal study where patients have been directly involved in the design of CD related research through a telephonic interview.

Choice of methodology:

The choice of a semi structured telephonic interview is well known to qualitative research including in CD (Ivarsson et al., 1999, Murray et al., 2004, Catassi et al., 2007, Da Silva et al., 2014). However this is the first time that a semi structured telephonic interview has been used in the design of an intervention for CD (Sainsbury et al., 2013b). None of the participants mentioned any adverse difficulty in telephone over face to face interaction, as felt by the author, hence, "facial anonymity" did not appear to affect the

quality of our data extraction (Hofisi et al., 2014), but this is an anecdotal observation and equally our research was related to a specific topic and was not researching in depth and/or over several broad areas.

The pilot interview phase (Paterson & Bramadat, 1992) in this research provided significant help in the smooth conduct of the research, such as with wording issues, and also with the timing of the subsequent interviews (Burke & Miller, 2001, Turner III, 2010). The initial phase guided the interviewer towards the possible intervention strategies, as the first phase used grounded theory of social research (Martin & Turner, 1986) and once the direction was fine-tuned the remaining interviews were conducted according to the predetermined topic guide.

Sample selection:

This study included only patients who were diagnosed on both serological as well as histological criteria. This is a clear strength of this study in terms of diagnostic objectivity, as suggested by earlier research (Watson, 2005, Green et al., 2005, Zevit & Shamir, 2014, Husby et al., 2012). It certainly reduces the pitfalls in the diagnosis of CD caused by the variable sensitivities and specificities of all individual methods of diagnosis (Dieterich et al., 1998, Brown et al., 2006, Robert, 2005).

Study population:

Guidance on the number of participants was drawn from previous studies (Biagi et al., 2009, Corrao et al., 2001, Ascher et al., 1997). The finally selected 80 patients (and interviewed 37 patients) compare well with published studies (Catassi et al., 2007, Sverker et al., 2005, Olsson et al., 2008) where interviewed population sizes ranged between 42 and 47. This, however, is not an absolute number as another study administered telephonic interviews to 215 patients (Murray et al., 2004), in our study we interviewed participants until no more new themes were emerging

There was a female predominance in the study population, which reflected the trend of CD in the general population, where the male to female ratio is 1:1.8 (Megiorni et al., 2008). This point has been explained in detail in relation to study I (Pages No 107-09). Another strength of our research is the inclusion of ethnicity data, which is novel in the sense that the author is not aware of any CD intervention that has included views from British Asians during the study design process, especially in such a robust manner. Themes analysis has clearly brought to the surface special issues in relation to diet, socialising and the

cooking environment, on the background of joint family systems and this has been detailed in a separate section below. Our study has started an in-depth exploration into the lives of British Asians, further comprehensive interviews would be of clinical interest. Whilst this area has previously been researched by questionnaires (Butterworth et al., 2005, Butterworth et al., 2004), these studies are now more than a decade old. The structure of the NHS has evolved significantly, and the affordability of CD treatment (a GFD) has been affected by NHS rationing. This may well affect the adherence level in all strata of patients.

Responders and return rate:

The return rate (53%) in this study is higher than that in study one, although the basis for this is multifactorial (Fan & Yan, 2010), it may be partly related to the length of documents/questionnaires the patients had to complete, which were clearly shorter in the latter and longer in the former and also the fact that they had volunteered to take part in study I. Additionally, one participant was given 50 GBP through a prize draw in study II. The impact of questionnaire length has been observed previously (Dillman et al., 1993, Edwards et al., 2004). Although monetary incentives in the form of a prize draw have a variable effect (VanGeest et al., 2001), we believe this may have played some role in the improved return rate in this study. There was no age, gender or ethnicity had any effect on return rate in this study (table 5).

Interview themes:

The technique of extracting themes through nodes using NVIVO® is an established method in qualitative research (Bazeley & Jackson, 2013). For this purpose, source documents (i.e. transcripts and field notes) were used (Patton, 2005). It is accepted that not all interviews were in English or completely in English, hence standardisation of data may be questionable, as a translator may infer different meanings leading to translation bias or dilemma (Temple & Young, 2004). But since the author speaks the relevant ethnic languages and translated the interviews himself into English, this effect is minimal.

It is also clear from the themes analysis that patients needed improvement in their education about CD as well as motivation to achieve adherence with a GFD. Both these areas were previously explored and later tried as an intervention in the previously explained study (Sainsbury et al., 2013b). However, it is noteworthy that web based training has a static approach and does not provide a patient centred

educational programme. In contrast it prescribes a blanket educational approach, not tailored to everybody's needs.

Telephonic clinic:

The majority of the participants declared telephonic clinics their intervention of choice and they were considered socially desirable. The telephonic clinics, according to the participants, are easily administered and this phenomenon was previously suggested by another study (Walker et al., 2011). They are, however, not without issues e.g. interruptions from family members and the inability to give visual prompts (Sturges & Hanrahan, 2004). The study relets in terms of choice of a telephonic clinic as a mode of intervention may be biased by the observation that since this data was gathered through a telephonic interview, hence patients may have opted for telephonic choice. It, however, is noteworthy that the participants in study II were selected from responder of study I through a process of randomisation to minimise this bias.

Although lack of non-verbal clues may affect telephonic interviews, the interviewer, however, was able to gather non-verbal clues during the interview process (e.g. sarcasm, tone of voice, interest level of the patient in the process) and manner of answering a particular question (e.g. seriousness, boredom or a feeling of urgency on the patient's part). High social desirability for telephonic clinics however must be interpreted with caution, as data gathered by telephonic survey has reported response bias, as suggested by previous research in this area (Chang & Krosnick, 2009, Holbrook et al., 2003, Kreuter et al., 2008). Chang & Krisnik (2009) reported that data gathered through telephonic means had comparatively more quantitative errors, satisfaction rate and relatively more social desirability response was recorded in comparison to online survey. Similarly, in comparison to face to face interviews Holbrook and colleagues (2003) reported that telephonic interviews gather more socially desirable responses. Similar observations were also reported by Kreuter and colleagues (2008). These biases were reduced by posing open ended questions and guidance was drawn from (DiCicco-Bloom & Crabtree (2006) and Qu & Dumay (2011)

The interview was regarded as private by the participants and that too has been suggested by a previous study (Mannino et al., 2007), but a later high powered study (n=465) suggested that a clear majority of patients (81%) had concerns about privacy during a telephonic consultation (Bahrani et al., 2017). This may be explained by the low power of our study population and more research is advised to explore this area. Privacy, was an important issue for patients in our research, as going to a sign-posted CD clinic

and sitting in an open waiting area gives rise to privacy issues. Privacy is a patient's fundamental right as per article 8 of the Human Rights Act (HRA) 1998. This issue was explored previously in the NHS by an interview based research and lack of awareness of the HRA was found amongst health care professionals (Woogara, 2005).

Privacy is of paramount importance to patients when it comes to personal and intimate health related issues, as suggested by an earlier study (Bull et al., 2001). Although it is accepted that CD is not a social stigma e.g. when compared to HIV (Kumarasamy et al., 2005) and other diseases, this area needs more research and patients' choices should be given preference in how they want to attend a clinic. This is only possible if more choices are available, such as telephonic clinics which offer relatively more privacy as compared to face-to-face clinics. It is acknowledged that telephonic clinics are not a valid alternative to face-to-face clinics in all clinical or research situations.

Patients considered telephone clinics to be pro-environment and this has been reported recently as well (Bahrani et al., 2017). Patients in our study showed environmental awareness and the impact of driving to clinic was not regarded as environmentally friendly. Although environmental awareness is not a novel concept, perhaps its awareness among CD patients may reflect the growing awareness among the general public in the past decade or so (Bohdanowicz, 2006), further consideration when designing patient services is warranted.

The traditional belief that, approaches other than face-to-face interactions lack the human touch (Ilieva et al., 2002) was not reported by the majority of participants in this study, apart from two who mentioned it in passing comments. Studies specifically designed to holistically investigate the differences between face-to-face or telephone clinic in patients with CD may bring some objectivity to these claims and may well remove this stigma from telephonic interactions between researchers and participants (Wasson et al., 1992).

The costs associated with of telephonic clinics are relatively small, this factor has previously been explored by Marcus and Crane (1986), where telephonic interviews were found to reduce cost by 75% which is (although low) still higher than our reported price. This is a decade old research and the cost of making a telephone call has reduced tremendously. Additionally, the role of telephonic clinic in qualitative research is not well established and it is less practiced as compared to face to face interviews (Opdenakker, 2006, Sturges & Hanrahan, 2004). Cost related to the telephonic clinic is an issue and

many studies have tried to quantify this in different settings, but no clear guidance can be drawn from the research as the issues dealt with were diverse. In relation to an osteoarthritis related telephonic service, no major difference was found with cost and the annual costs were $70.86 and $31.00 per unit improvement in physical functioning and pain, as suggested by a US based study (Weinberger et al., 1993). Similarly a later study involving telephonic support for heart failure patients found this method to be cost effective (Clark et al., 2007). Likewise, nurse operated telephonic triage lead to a saving ranging from €22.2 to €70.2 (Marklund et al., 2007). Detailed economic analysis of a telephone clinic service would be warranted.

Coeliac disease day conference:

The idea of a CD day conference was accepted universally by the White Caucasian participants. Although patient education is a regular event and conferences are arranged for this purpose by patient advocacy groups such as the Coeliac UK, there have been no specific studies looking into the effectiveness of these conferences, especially in ethnic populations. We report low interest in such group teaching from our South Asian community, but this area may be looked into by ascertaining causes of low interest. Conferences do however carry educational value, as suggested by an HIV conference which seemed to improve patients' adherence to anti-retroviral therapy (Rueda et al., 2006), but the seriousness of HIV is evident to patients and physicians and this effect cannot be generalised to CD. It is not entirely clear why the majority of Asian patients were opposed to the idea of attending a CD conference day, but this area needs in depth interview based research. Other issues raised by the patients were travel related and participation anxiety. On the positive side, group meetings were within the experience of the majority of the White Caucasian population.

Attendance at such meetings is high only for motivated patients and previous research has identified characteristics which define poor attendance, such as: lower social class, unmarried patients and the amount of time taken to reach the event (McClure et al., 1996). One of the issues however demands special attention and that was parking, which appeared as a recurrent theme in this study. Previous research has also indicated that availability of parking is a key issue for patients in attending an event (Avis et al., 1995, Penneys & Glaser, 1999, Ackerman et al., 2013) and reimbursement for parking or arranging transport seems to improve attendance (Ackerman et al., 2013). It is thus inferred that, in order to improve attendance, parking is a key factor to be kept in mind.

Standard extended clinic and dietitian appointment:

This option was liked by the majority of the non-adherent patients and such clinics, when offered in conjunction with a dietitian, improve adherence to a GFD, as suggested by previous research (Hall et al., 2009, Addolorato et al., 2004). However, it is not clear if increasing the length of time per patient from 20 minutes to 60 minutes would have any effect. This issue was previously noted to have no significant effect (Eide et al., 2003), but the clinical setting was an oncology clinic and the finding cannot be easily generalised to CD; specific research must be conducted. Another well designed study (n=99) and detected an improvement in adherence to GFD while under dietitian follow up (Wylie et al., 2005) and although our power (n=37) is less as compared to this study, the inference is the same. A year later Bebb et al., (2006) arrived at the same conclusion but another study (n=413) reported no significant relationship between dietitian follow up and adherence to a GFD (Mahadev et al., 2013). The latter study however had a significant proportion of patients (39%) who had seen the dietitian only once, hence, were not followed up by the dietitian. Our study is not conclusive in this area partly because we did not explore this area as an aim of this study but our results do follow the well-designed studies and it may be inferred that dietitian lead clinical follow up do inprove the adherence to a GFD especially in view of a intervention study by Rajpoot et al., (2015).

The issues of parking and privacy raised by the patients have been explained above, but special issues were raised about car parking machines and the punitive nature of the Trust for over-parking. This is an interesting area and may well be linked to patients' inability to attend to other clinics. Survey and interview based research needs to be conducted to explore this area further. Similarly, waiting time was one issue that patients did not like about CD outpatient clinics and research has shown that this indeed is one major factor for patients' dissatisfaction about clinics (Huang, 1994, McCarthy et al., 2000) and correcting this actor may improve satisfaction (from 50% to 74%) among patients (Eilers, 2004). Outside the NHS, in a private setting, this is not a major issue, as there is a smaller gap between referral to the physician and the appointment (Roll et al., 2012). It may thus be argued that, provided there are no cost implications, a longer clinic duration with preferably a shorter waiting time, would not only improve adherence to a GFD but also patient satisfaction.

Web based teaching:

The approval rate for web based intervention was 31% as patients were not clear about the way in which a web based methodology would work. They also insisted on videos rather than “dry slides.” This is understandable, as this is a technology dependant intervention and necessitates internet access. The Australian based web intervention (Sainsbury e al., 2013b) showed significant improvement in adherence scores to a GFD, the study was conducted on a cohort selected from the Coeliac Society, which tend to show better adherence as shown by study one and an earlier systematic review (Hall et al., 2009). Additionally, the ethnicity of participants was not reported and the programme was only available in English. It is recommended that the applicability of “Bread and Butter” (Sainsbury et al., 2013b) should be confirmed in a multi-ethnic population who are diagnosed on objective criteria with input from patients in the design of the course. Web has also been used to deliver a Webinar (Loucka, 2018, Case, 2013), a seminar conducted through internet but the acceptability of Webinar has not yet been assessed in well-designed research studies apart from a study (n=7) where five patients considered this to be an acceptable method of patient related education is end stage lung disease. More research is needed to evaluate this area.

Other Themes:

Home visits were not liked by the patients and only few patients were happy to accept that. The main issues were patient availability and privacy. One previous study confirmed the effectiveness of home education in improving self-care in cardiac patients post discharge (Jaarsma et al., 1999), but the study also used in-patient care and education, so it is not clear how big a part the home visit played in improving the outcome. A similar study with much improved methodology was conducted a few years later and home visits were found to be effective in improving outcome in heart failure patients (Krumholz et al., 2002). The author reported that this issue was sensitive for a few patients and it was not explored in detail, but the exact role of home visit in CD needs further research.

Email was favoured as an intervention by very few patients and its effectiveness in patient care has been questioned in the past by a randomised trial, which concluded that email was an ineffective strategy (Katz et al., 2003). Similarly, Haas et al., (Haas et al., 2017) evaluated text messages as an intervention strategy and found it in effective in increasing adherence to a GFD.

It may thus be concluded that email on its own is ineffective and not favoured by the patients, but may well have a role along with other modes of intervention. Similarly, none of the patients favoured an information booklet on its own as a mode of intervention. The impact of booklets has not been researched in CD, but their role in pre-operative anxiety was not found to be significantly useful (Gillies & Baldwin, 2001), although several other studies have found them useful (Frederikson & Bull, 1995, Giraudet-Le Quintrec et al., 2003, Gold & McClung, 2006, Deakin et al., 2006). Interestingly, almost all of the participants liked the idea of an information booklet as a supportive material. It is thus concluded that patient leaflets should be an adjuvant to other interventions.

Only three patients were interested in watching DVDs although previous research has indicated the usefulness of DVDs (Meilleur & Littleton-Kearney, 2009), it is argued that trends are changing and patients are more interested in watching YouTube® rather than DVDs (Stellefson et al., 2014, Gabarron et al., 2013, Fat et al., 2011). In conclusion, themed analysis of this study supports the use of a well-structured telephonic clinic with supplementary leaflets. This intervention would appear to be the most cost effective; time efficient; respectful of patients' privacy; useful and convenient.

Comparative analysis:

A comparison of the eight suggested models of delivery shows that the CD day conference and telephonic clinic were particularly favoured by the participants, followed by standard clinical appointment and dietitian clinics and this may be based on several factors. Firstly, cost to patients was assessed in relation to the different models and patients found the costs of telephonic clinic, home visit, text message and leaflets negligible. The CD day conference was assessed to be the most expensive choice, followed by standard clinics. Although the causes behind this were not explored, a combination of parking costs, travel expenses and possible conference costs might have been in the patients' minds. This is an interesting area in terms of patient centred care and needs further exploration.

Secondly, the usefulness of the mode of intervention was assessed using the same technique and the CD day conference was considered most useful by the patients. This brings to the surface a discrepancy between the CD day conference was not liked by all patients, whilst the majority recognised its importance in terms of usefulness, hence this may be related to a group effect (Johnston & White, 2003, Barsade, 2002). This area also needs more research, as if the cost implications could be met, then this might well turn out to be the best choice. Other useful models in this context were: telephonic clinic,

leaflets and standard clinic; the least useful was considered by patients to be the home visit. This is interesting as leaflets on their own were not favoured as a mode of intervention, but were considered useful by the patients. It may thus be argued that leaflets could be part of an intervention. Home visits were considered the least useful and although research has shown benefits of home visits in heart failure (as stated above), our sample reported concerns with home visits, which may be particular to patients with CD and not represent the views of patients in general. This is also an important area to be researched, as any future intervention may or may not have to exclude home visits altogether in relation to CD.

Thirdly, potential of the mode of delivery to lead to sustained change in behaviour was explored and all but home visits, text messages and multimedia were seen favourably by the patients. None of the modes of delivery had more than 50% approval, which either reflects pessimistic viewpoints on the patients' part, a common finding in chronic or incurable disease (Wildman et al., 2007, Schulz et al., 1996), or this area may be truly multi-factorial and training and education may only play a part in sustained behaviour improvement. Fourthly, in terms of knowledge, again the CD day conference was ranked highest, followed by the telephonic clinic. This area again will need high powered in-depth interview based research to ascertain the true ranking of these modes of deliveries. It may also be inferred that probably one type intervention may not be suitable for all patients and it has to be tailored according to age, ethnic background, level of education and personal preferences of the patients. .

Finally, it is quite clear from the overall ranking and subsequent quantitative data, that most of the participants would prefer a course which has reduced costs to them, but at the same time has the advantage of improving knowledge and the potential for behaviour change.

In conclusion, this study has reached an opinion that the best design for this set of patients is a telephonic clinic to increase the knowledge of non-compliant patients and to motivate them to improve their adherence to a GFD. This was accomplished in the next phase of the PhD.

Comparison of White Caucasian and South Asian ethnicities:

CD is a global disease and affects both White Caucasians and South Asians. Two seminal studies addressing this issue (which used questionnaires in a slightly different fashion) are more than a decade old (Butterworth et al., 2004, Butterworth et al., 2005). Our study was unique in examining a group of patients who were non adherent to a GFD, through a mixed methodology. Additionally, it is also

accepted that the catchment population of our hospital is just as ethnically diverse as those in the above studies, although the power of our study (n=7) is lower as qualitative interviews were undertaken to saturation of themes.

Knowledge about CD:

Several aspects of knowledge about CD came to the surface, including: understanding information given by the dietitian and clinician, sufficiency of information, comprehension of information and uniformity of information about CD. There was variability in the responses from both ethnicities, but since this multifactorial area needs deeper exploration with focused questions before conclusions may be drawn. The sufficiency in terms of the level of knowledge about CD was similar between the South Asians and White Caucasians in this study. It is, however, accepted that our questions were measuring the horizontal knowledge as compared to the vertical and in-depth knowledge about clinically important aspect of CD. This is important, as knowledge about CD is an independent factor for adherence to a GFD (Halmos et al., 2018). However, the construct “knowledge” covers a wide spectrum and may mean different things to different patients, ranging from the pathophysiology of CD to the identification of GFP. Several questionnaires have been developed, but a particularly effective one was created by Silvester and colleagues (2016). Their questionnaire directly tests patients’ knowledge about the presence or absence of gluten, by getting them to label items as permissible or non-permissible. This questionnaire is used in study 3 of the PhD.

Problems in following a GFD:

Certain issues were common to both ethnic groups, such as the availability of GFP and the cost attached to them. Additionally, the taste of GFP and lack of motivation to follow a GFD,, lead to decreased adherence to a GFD. These views are supported by published studies (Hall et al., 2009, Errichiello et al., 2010). Socio-cultural dietary differences between Caucasians and other ethnicities have been researched previously (Mumford et al., 1991, Kelemen et al., 2003, Counihan & Van Esterik, 2012, Simmons & Williams, 1997) and our study also reported differences between these two groups. However, this is a separate and evolving research area, as South Asian populations integrate into western society and westernised food habits are adopted, such as increased fat and meat intake (Wandel et al., 2008, Aloia et al., 2013). Among Asian patients, interestingly, there are unique issues that might be related to the way food is prepared and served in the Asian household, this has been previously described (Counihan & Van Esterik, 2012). All Asian patients (n=9) from our study were

served warm meals cooked at home from fresh ingredients on a daily basis and consumed *ensemble* on most weekdays. This is in contrast to the previously reported research where increasingly westernised food consumption was noted amongst South Asians (Holmboe-Ottesen & Wandel, 2012, Wandel et al., 2008).

The majority of South Asians reported to eat at home and this is a known cultural trend (Aloia et al., 2013) which also follows the previously reported trend (Goyal & Singh, 2007) and the reasons are multifactorial, as previously researched in relation to type 2 diabetes (Lawton et al., 2008, Stone et al., 2005). Our study is unique in reporting this trend in relation to CD in a similar fashion. It does highlight the practical importance of dietitians who are advising South Asians keeping in mind these cultural trends when explaining GFD.

Our study included mostly with first generation South Asian people (based on the fact that they were born outside the UK) and the previously reported trend may well be affected by the age of participants. It is postulated that younger and second generation South Asians are more integrated, hence westernised to consume high energy and high fat food (Holmboe-Ottesen & Wandel, 2012, Wandel et al., 2008, Namvarasl & Chakravarty, 2018). It is accepted that this area is complex, multifactorial and shrouded in cultural and social layers.

White Caucasian participants reported reasonable confidence in restaurants to serve GFP, but South Asians did not show comparable confidence. Although food served in restaurants may well be GF, this issue again has a cultural specific. South Asians have less confidence in the restaurant staff and this is related to perceptions of South Asians about restaurant food. This issue was previously researched by Aloia and colleagues (2013) and they suggested that the reasons were multifactorial such as convenience, price, social enjoyment and quality of meals. Interestingly, the perception of the South Asians can be supported, as there is some evidence to show that restaurant chefs have less knowledge about CD than patients with CD (Karajeh et al., 2005). It is felt that awareness of CD might well have changed and more qualitative and qualitative research is needed in this area to explore the reasons behind this issue. This again will influence how we advise patients with CD about eating out at restaurants; at present they consume restaurant food less frequently as compared to home cooked meals (Zarkadas et al., 2013, Zarkadas et al., 2006).

Our study reported universal issues of poor adherence to a GFD while travelling and at a friend's house. This trend has previously been reported by Zarkadas and colleagues (2006), where patients with CD

were found to avoid travelling (38%) because of their illness. We, for the first time, have reported that significantly more South Asians avoid travel as compared to White Caucasian patients with CD. It is felt that this area again is multi-factorial and possible issues may include availability of GFP and / or preparation of GF meals pre travel and more research is needed for effective dietary advice for CD patients while travelling.

Our study reported very low availability of GFP in local Asian stores and that was reported to be poorer compared with the main supermarkets. Although a general trend of poor availability (41%) of GFP was reported by Singh and colleagues (2011), since then general awareness has increased and so has the availability, as reported by a later study (Burden et al., 2015). Recently, another UK based study has reported good availability of GFP (Hanci & Jeanes, 2018), However, in all the studies there was limited availability in local convenience stores but the differences may be explained by the methodologies i.e. interviews and questionnaire based studies. That is perhaps why our study reported good availably (88%) of GFP.

We have reported sparse availability of GFP in Asian stores. One reason behind this might well be the cost, as a GFD is four times more expensive than a normal diet (Burden et al., 2015). However, lack of knowledge about CD among store owners and low numbers of regular customers with CD, might be other factors which deter Asian store owners from stocking GFP. It is felt that again this area needs a well-designed study including all stores ethnic groups purchase their food from.

Limitations of the research:

Firstly, the manner in which the data was collected (through telephonic interviews) and the inevitable lack of face-to-face interaction but, it is acknowledged that perhaps Skype® based interviews might solve this issue to some extent and it is thus recommended it is offered to patients if similar research is being conducted, a visual medium could be considered, as access to the internet is improving in the UK and worldwide (Poushter, 2016) and Skype® is increasingly being used in qualitative research interviews (Hanna, 2012, Janghorban et al., 2014).

Secondly, the analysis of qualitative data in social science is equivalent to “impression analysis” in forensic science, where trace evidence leads to reconstruction of the scene and inference may differ depending on how that is arrived at (Welsh, 2002). This area has been debated for both reliability and validity in relation to such analysis (Kelle & Bird, 1995), but outside this discussion there are well documented research studies using qualitative methods.

Thirdly, the interviews were conducted in 20 to 30 minutes, which might be considered insufficient time to obtain data about choice of intervention, but it is clear from the methodology that the initial 13 pre-interviews gave sufficient guidance to the authors about the questioning strategy and obtaining maximum information in a limited time (Burke & Miller, 2001). Time is an essential element and information obtained is directly proportional to interview length. Although it is acknowledged that high power may bring diversity, the purpose of this research was to gather a reasonable amount of information from patients, in order to design an intervention which was both cost effective and time-efficient. It was not our purpose to explore every possible and rare way an intervention could be designed and, keeping in view the previous research, this sample size was sufficient for qualitative research of this type (Marshall et al., 2013, Francis et al., 2010). Additional time before the interview for patients to consider the pros and cons may have helped to gather more informed decisions from participants. Fifthly, our study focused on adults and thus the preferences for paediatric age group were not explored (Maki et al., 2003). Their choices may be different from those of the adult population and finally it may also be inferred that using telephone as a medium to data about choices of intervention which also includes telephonic intervention is a potential bias.

Despite limitations, as explained above, “Your View” has given a unique view of a multi-ethnic population to inform the design an intervention aimed at increasing adherence to a GFD. Whilst acknowledging its limitations, this study has strengthened the view point that patients are valuable assets in all aspects of the treatment and management of chronic diseases, including the design of interventions/ service development. In conclusion, telephonic clinic informed by published studies and the qualitative interviews will be developed and evaluated in study 3.

Chapter Four

SECTION I

Study 3: Intervention to Increase Adherence to a Gluten Free Diet (REST-Gluten)

Introduction

To date there are only eight intervention programmes reported in the literature stating an intervention to improve adherence in relation to a GFD and only three of them report direct data on improving adherence to a GFD. Studies have either targeted behavioural aspects (Addolorato et al., 2004, Ring Jacobsson et al., 2012) to indirectly improve adherence to a GFD, or have used follow up models (Pekki et al., 2018, Rajpoot et al., 2015) to assess the role of follow up in clinics in maintaining or improving adherence to a GFD; recently a well-designed study examined the role of text messages in 12 to 24 year olds to improve adherence to a GFD (Haas et al., 2017). Sainsbury and colleagues (2015, 2013b) used a web based intervention to improve adherence to a GFD in a study population derived from social media and Australian Coeliac Society members. A recent study (n=118) examining the role of a smart phone app in the management of CD has been reported, but it is not directly related to increasing adherence to a GFD, hence excluded (Dowd et al., 2018).

Detailed critical review of the aforementioned studies can be found within Chapter One and suggests that there are methodological deficiencies in these studies as, for example, increased adherence is associated with membership of coeliac advocacy groups (Hall et al., 2009, Muhammad, 2013), thus introducing selection bias in the latter study (Sainsbury et al.,2013b). Additionally, web based methodology is dependent upon computer literacy and additional associated costs might well be an issue in an elderly group which forms a significant proportion of the adult UK CD population (West et al., 2004). Furthermore, intervention studies in this area (Sainsbury et al., 2013b, Haas et al., 2017) have predominantly used a cohort with CDAT score below 13, thus already adhering to a GFD. Despite these shortcomings, the study provides both a theoretical as well as a practical baseline for future design and execution of studies in this under researched area.

It is quite clear from the literature review in Chapter One that intervention to increase adherence to a GFD is a minimally explored area and there is a need to design an intervention which is: not substantially

dependant on technology, cost effective for patients as well as health care providers, easy to administer and not geographically bound; above all is designed with direct input from patients. One way of conducting this research would be to recruit patients from a hospital data base, diagnosed on histological grounds to minimise selection bias, with a proportion of them being from ethnic minorities so that the intervention designed is generalizable and clinically relevant. It is evident that no intervention to date has been reported in the UK population, which compared to Australia has a different demographic.

The PhD will be using a telephonic clinic as an intervention and it is one of the accepted and well established ways of interacting with patients to gather quantitative data (Aday & Cornelius, 2006, Barriball et al., 1996, Carr & Worth, 2001); additionally, it is used extensively in social research (Bernard, 2011). Perhaps as a cultural trend, face to face contact is preferred over telephonic conversation (Garbett & Mccormack, 2001, Marcus & Crane, 1986). In addition to that, Telephonic interview can also affect survey outcomes such as data quality, as reported by one study (Aquilino, 1994). Although no extensive comparison with face to face interviews has been conducted to assert the superiority of one mode of practice over another, there is a suggestion that face to face interviews may improve the quality of data, as shown by a later study (Moum, 1998). It should be pointed out that data quality in qualitative interviews is multifactorial (Bryman, 2003) and is affected by both interviewee and interviewer related factors (Patton, 2005).

Telephonic interview is an economical alternative (McHorney et al., 1994, Chapple, 1999), as it cuts down costs of travel and increases access to wide geographical areas (Sturges & Hanrahan, 2004). Although loss of non-verbal and contextual data is a potential issue (Burnard, 1994), telephonic interview for this piece of research was selected according to participants preference. More importantly, no significant evidence exists to suggest that the loss of non-verbal and contextual data will affect the quality of data gathered, especially in this type of research. The table below (Table no 11) compares telephonic and face to face interviews to clarify the reasons why telephonic interview was selected for this study. The table below summarises and compares the characteristics of both modes of interview (Table No 46).

Table 46: Comparison of two modes of interview: telephonic vs face to face.

Characteristics	Telephonic		Face to Face	
	Positives	Negatives	Positives	Negatives
Related Cost	Less	--	--	More
Access to patients	Wide geographic	--	--	Restricted
Privacy	Reasonable	--	--	Reasonable
Flexibility	More	--	--	Less
Body language	--	Absent	Present	--
Human touch	--	Lost	Present	--

This PhD aims to recruit patients directly from a hospital database and our intervention will involve a telephonic medium which is relatively less technology- and literacy-dependant than computer based teaching. The ideas from a review of the literature, including of the Sainsbury and Mullen (2013) study, were refined by involving CD patients as detailed in Chapter Three REST-Gluten, the third study in series in this PhD, aims to fill the methodological gaps in the previous studies and focus on the non-adherent patients along with a control group, to assess the efficacy of a telephonic intervention in increasing adherence to a GFD. Additionally, it is the first study which specifically aims to improve GFD adherence in the UK.

Study Aim:

To explore the role of telephonic clinics on adherence to GFD in adults with CD by conducting a semi-structured telephonic clinic and to assess if post intervention adherence to GFD is significantly different than pre intervention. In addition, it is also aimed to see if delivering such an intervention will affect knowledge about CD in the patients as measured Silvester's questionnaire (2016). Furthermore, this study aims to see the impact of a telephonic clinic as an intervention on HRQoL as measured by CDQoL score (Crocker et al., 2018b).

Study Hypothesis:

The hypothesis for this study is non-directional (two tailed) and the null hypothesis (H0) for the study is that there will be no significant difference between adherence to a GFD, knowledge and quality of life in pre and post intervention groups. It may thus be stated that the independent variable i.e. telephonic clinic will have no effect on the dependant variable i.e. CDAT, Silvester and CDQoL scores.

Method

The study was conducted using a telephonic intervention in a prospective controlled manner and the instruments used to measure the effect were: CDAT score (Leffler et al., 2009), Silvester CD knowledge score (Silvester et al., 2016) and Crocker CDQoL score (Crocker et al., 2018b). One to one telephonic conversation was used to add a human touch to the research and make it interactive and more acceptable to patients based on patients' choice of intervention.

The suitability of this design is evident from the universal acceptability of this methodology among the intervention patients and as previously suggested by the study II cohort in their interviews. In clinical practice, due to the complex nature of human disease patterns, a particular ailment (CD in this case) may be pathologically similar in a group of patients, yet affects the patients very differently. Telephonic conversation represents an inferior level of human interaction as compared with a face to face meeting, but, as suggested by the patients in study II, it is acceptable, cost effective and convenient for them, hence accepted as a study design.

Inclusion and Exclusion Criteria

All adult patients (18 years and above) diagnosed with CD on confirmed histological grounds and within the CD database held within the dietetic department of the Dudley Group of Hospitals (DGH) were selected for this study. In addition, for standardisation of diagnosis, only patients who were diagnosed by the DGH pathologists were included in this study. Moreover, for consistency in treatment and dietary advice received, only patients who were under the follow up of the DGH consultant gastroenterologists and dietitians were included. Similarly, all patients below the age of 18 were excluded. In addition, all those who were not under DGH follow up were also excluded for ethical reasons (as the local Research and Development office approval was only applicable to DGH related patients), plus the standardisation issue as explained above. Furthermore, patients with learning difficulties, problems filling in forms and

questionnaires, living outside the geographical area of Dudley and those who were diagnosed by non DGH pathologists were excluded from the study.

Participants

Participants for this study came from the CD database of the dietetic department of the DGH. Considering the number of available patients, a convenience sampling method was used (Farrokhi & Mahmoudi-Hamidabad, 2012, Marshall, 1996) and all eligible CD patients were approached via postal invitation after applying the inclusion and exclusion criteria.

Sample size:

Research has shown a modest effect from telephonic based interventions, in promoting healthy dietary behaviour in participants without CD, as shown by a systematic review (Eakin et al., 2007). Therefore, based on two tailed hypothesis a-priori power analysis was done (d = 0.5; 80% power; α = 0.05) and it was shown that 128 participants will be required to detect a statistically significant difference in change of behaviour between the groups. A meta-analysis, examining psychotherapy on symptoms of depression, concluded that keeping in view the significant heterogeneity in attrition across these studies ($Q = 32.43$, $p = .0006$), the mean attrition rate was 7.56% (95% CI = 4.23–10.90, $p < .0001$) and allowing for this, the desired sample size was 138 (Mohr et al., 2008). Additionally, a previously conducted intervention by Sainsbury and colleagues (2013) reported a significant improvement in CDAT score in participants (n=26) who completed three months follow up. Moreover, based on the previous return rate of 39% (Muhammad et al., 2017), the expected available sample was 75, with 28 expected non adherent patients, which matched well with the previous intervention by Sainsbury and colleagues (2013).

Design

Pre intervention:

All patients were sent a research pack containing: CDAT (Appendix 1.1D) as an adherence instrument, DASS questionnaire (Appendix No 1.3H) to exclude participants if evidence of subclinical depression was observed, CD quality of life questionnaire (Crocker et al., 2013) to assess HRQoL (Appendix no 1.3I) and CD knowledge questionnaire (Silvester et al., 2016) to assess patients' knowledge about a gluten free diet (Appendix No 1.3G). Additionally, a change in circumstances form (Appendix no 1.3J)

was also sent to ensure that the possible effect of known factors (Hall et al., 2009, Flaherty, 2014) which may affect adherence to a GFD were also monitored.

Planned Interventions

The telephonic clinic targeted both knowledge and motivation components. One hour telephonic clinics were administered as an intervention (explained below). A leaflet as a guide to the discussion in clinic was posted to all those patients who were selected for interview (Appendix No 1.3D). Selected patients were asked about their stage of behavioural change at the very beginning of the clinic, as per guidelines drawn from Prochaska and colleagues (Prochaska et al., 2008) (Appendix no 1.3K). The steps of the intervention are explained in the figure below (Fig No 32).

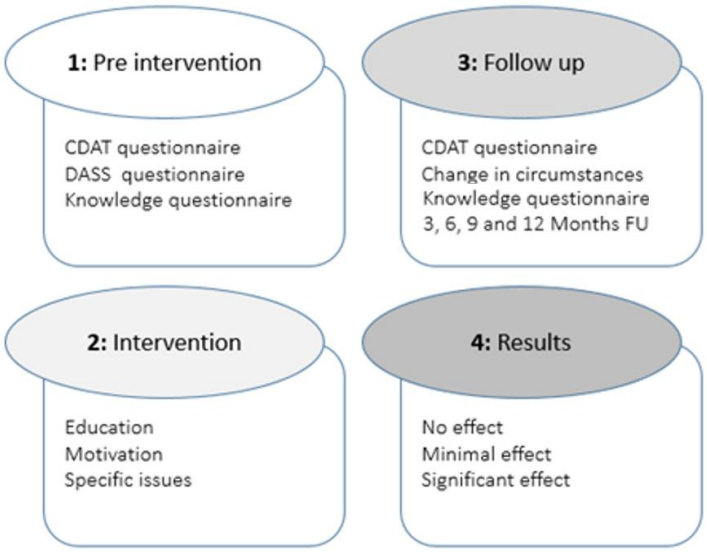

Figure 32: Study Three process

Groups for Intervention

Based on a review of the literature and the PhD study II "Your View" as explained in the earlier section, the intervention for increasing adherence to a GFD was designed as a prospective trial using two arms. The first of these was the Non-Compliant Intervention Group (NCIG) with the aim of recruiting 50 patients who were non-compliant with a GFD. They agreed on a schedule time for the telephonic clinic intervention which lasted for approximately 1 hour. Three months after the telephonic clinic they were requested to complete CDAT, CD related quality of life, CD knowledge and a change in circumstances questionnaire. They were followed up at six months and requested to complete the Leffler and a change in circumstances questionnaire. The second group was the Adherent Non-Intervention Group (ANIG)

with the aim of recruiting 100 patients (randomly selected from the patients' adherent to a GFD. This was the adherent control group and they did not receive any intervention. Three and six months after the pre intervention questionnaires, they were requested to complete the Leffler, CD related quality of life, CD knowledge and a change in circumstances questionnaire.

Intervention

Leaflet design and contents

The telephonic clinic followed the format of a leaflet which was sent to the intervention arm of the study in advance (Appendix 1.3D). The contents of the leaflet were based on the "Your View" study, where certain themes related to knowledge gaps, behavioural issues and difficulties had been highlighted by participants. Written information or leaflet (Raynor, 2018, Dickinson et al., 2001, Grime et al., 2007) was favoured by patients as a medium of education in the "Your View" study, but in combination with some other form of interaction e.g. telephonic interview rather than stand alone. Although there is no evidence of using a leaflet in relation to adherence in CD, the leaflet for this purpose was designed based on prior research, as health-related leaflet design has evolved significantly since its first introduction in the UK in the mid-80's (Coulter, 1998, Boundouki et al., 2004).

Characteristics of the coeliac disease leaflet

Research has emphasised the benefits of including pictures within leaflets, to increase readers' attention to and recall of health education information (Houts et al., 2006, Mansoor & Dowse, 2003), hence our leaflet was mostly in pictorial form. Care was taken not to use too much technical information and at the same time not to make it too simple; rather a conceptual pictorial approach was used to gradually build up information for the topic (Collier, 2011). The majority of the pictures were coloured, as this enhances learning when compared with black and white pictures (Rankin et al., 2005). All pictures were selected from Google Image® and are in the public domain.

Cultural diversity was kept in mind (Herbert, 1997) and this was supported by translating the information into respective different languages (Urdu, Pashto, Punjabi, Arabic, Persian, Hindi and Gujarati) with a view to increasing comprehension and interest in the leaflet (Dickinson et al., 2001, Kumar et al., 2004). Extreme care was taken to avoid any generally offensive, racially tabooed or culturally non permissible

elements in the leaflet. The leaflet was divided into short topics and the contents of the leaflet are summarised in the table below (Table No 47).

Table 47: leaflet for intervention

Topic	Area targeted	Contents / comments	Behaviour
Normal abdomen	Knowledge	3 pictures of normal abdomen. Basic theme to build up discussion.	Attitudes, perceived behavioural control.
Coeliac disease	Knowledge	3 pictures with gradually increasing complexity about the pathology of CD starting from inflammation to mal-absorption	Attitudes, perceived behavioural control.
Gluten causing symptoms of CD	Knowledge	3 pictures showing gluten containing food. They were kept simple and included cultural elements along with general information about gluten	Attitudes, perceived behavioural control.
Symptoms of CD	Knowledge	4 pictures showing the most common symptoms in pictorial form. Care was taken not to include any potentially distressing pictures.	Attitudes, perceived behavioural control.
Complications of CD	Knowledge behaviour	3 pictures of the most common complications.	Attitudes, perceived behavioural control. subjective norms
Gluten free food	Knowledge	1 picture. General over view of gluten free diet	Attitudes, perceived behavioural control.
Barrier to adherence	Behaviour	Educate about behaviour modification, working on coping mechanisms, counselling and support.	Perceived behavioural control, subjective norm, attitudes, psychological symptoms, coping
Specific issues	Misc.	Two pictures; cross contamination of gluten and how to avoid, tips on preparing meals. Issues with eating out. Instructions on assertive behaviour and putting health first.	Perceived behavioural control, attitudes, subjective norm, psychological symptoms, coping

Contents and delivery of the telephonic clinic

The clinic followed a similar format to that of a normal face to face clinic in an outpatient department. For the purpose of standardisation, a specific format was followed and this was rehearsed before the actual interaction with the patients. The components of the telephonic clinic were as follows:

Introduction and clinical rapport

Each clinic started with a telephone call on a number provided by the patient and at the time agreed (Appendix No 1.3L). Clear introduction of the researcher and the related professional role was followed by an explanation of the purpose of the clinic; guidance in this regard was drawn from previous studies (Dang et al., 2017, Ali & Elzubair, 2016). Patients were encouraged to speak early in the course of clinical conversation and any anxiety detected was addressed at that point by providing reassurance. Patients were specifically encouraged to ask questions, even if that meant interrupting the conversation at any point during the clinic. Patients were asked (in very simple and non-judgemental language) about their diagnosis and if they understood their test results when first told the diagnosis of CD. Patients were then asked about their treatment goals and expectations from the telephonic clinic; a clinical agenda was set and patient autonomy was fully respected (Lee & Lin, 2010).

General advice

All patients were strongly recommended to either join or maintain membership of Coeliac UK. Additionally they were advised to ensure they had access to GF foods and, if their local stores lacked such products, the best ways to approach the store manager. They were advised to stay in touch with the hospital dietitian and keep their physician and dietitian appointments. For events of a temporary nature, such as travelling or being a guest in a friend's house, patients were advised to take, e.g. some GF sandwiches with them, if unsure about access to GF foods. Furthermore, issues with the texture of GF foods were acknowledged to be a universal issue and patients were advised to contact the manufacturer of such products in order to guide them. It was however acknowledged that this was a difficult area, as there were ceilings in relation to costs and availability of palatable products.

A subset of patients, who expressed cravings for gluten containing foods, were given advice about reducing their intake gradually i.e. from daily to weekly to monthly with an aim of stopping altogether. Patients were advised to keep a food diary for trigger events which may lead to dietary transgressions.

Additionally, they were advised to read about success stories and reward themselves on maintained behaviour. Last but not least, a six monthly audit was advised to record the episodes of transgressions and to self-motivate to close the gap between theory and practice. Participants were then invited to comment on specific issues that influence their adherence to a GFD, which may or may not follow general themes.

Knowledge about CD

The attention of the patients at this stage was drawn to the different components of the leaflet, which were explained using a tailored educational strategy, the guidance for which was derived from previous research (Deakin et al., 2006, Coulter & Ellins, 2007, Oliver et al., 2001). Although the teaching method by default was one to one (Harris, 1986), the method of delivery used in this section was learner centred (Bender, 2016) and content focused (Desimone, 2011).

Firstly, referring to the first picture on the leaflet, a general overview of the food we eat was given, along with a brief outline of the anatomy and physiology of digestion. Here it was emphasized that different components of food are absorbed differently and wheat is one of the important components in the diet. Secondly, referring to the next two slides on the leaflet, a detailed outline of CD was given to the patients, which included the structure of the small intestinal villi and the concept of surface area available for absorption.

They were then told how wheat, a harmless component of the food for others, damages the villi of the small intestine in patients with CD, by drawing their attention to the flat villi on the slide. At this point the concept of inflammation caused by the immune reaction against gluten was introduced and this was linked to the previous slides on normal absorption; they were further told about the effect of flat villi on the general absorption of food. Furthermore, inflammation leading to pain in the abdomen in some (but not all) patients was introduced here, as shown on slide number two on the leaflet.

Discussion about gluten and gluten containing food continued at this stage, with a tailored explanation based on the patient's GF food knowledge score (which had already been checked through the knowledge questionnaire) (Silvester et al., 2016). Patients were given a brief outline of GF foods (Gallagher, 2009) and their attention was drawn to the resources available such as Coeliac UK (Coeliac UK, 2015). Patients were individually advised about a GFD and were encouraged to keep a diary (or where applicable a smart phone based list) of commonly used gluten containing foods and how to avoid them (Case, 2005).

Next, a brief sketch of the symptoms of CD was given. Looking at slide number four and linking it to the previous slides, it was emphasised that symptoms were not always present, despite the fact that the intestine was inflamed. Allied to this concept, common and less common symptoms of CD were briefly explained and a detailed discussion about the patient's current or past symptoms (if any) was undertaken. The discussion then moved on to common complications (slide No 5) such as anaemia, bone fragility and related fractures, along with effects on health related quality of life such as: tiredness, anxiety and depression; the economic impact of CD was also discussed.

Following this, the pace of the interview was slowed down and the patient was informed of the possible complications of long term inflammation in the small bowel which may result in changes to cells and may lead to cancer in a minority of patients. This was followed by a pause and the patient was asked to briefly repeat what had been said so far, to check engagement and understanding. Questions, if any, were answered and areas were discussed again if there was any doubt.

Then, likening it to the previous concept of gluten containing foods, the idea of a completely GF diet was introduced (Slide No 6). Linked to this concept, the presence of hidden gluten was introduced and how to recognise it by reading food labels in a logical and methodical way (slide No 7). By virtue of its practical importance, this part was deliberately prolonged and the three most common international signs of GF food were referred to (and were printed in colour in the leaflet).

Patients were then told where to look for nutritional information: that it is often displayed as a panel or grid on the back or side of packaging and usually contains information about energy and dietary contents such as fats, carbohydrates and proteins. Additionally, their attention was drawn to the nutritional information present on the front of the packaging which comprises different food groups at a glance along with colour coding.

Certain exceptions, where food has been processed and the gluten removed, were also mentioned at this stage (e.g. wheat starch). We also highlighted that labelling such as "may contain traces of gluten", "made on a line handling wheat", "made in a factory also handling wheat" does not necessarily mean that the product is contaminated with gluten. If unsure, patients were advised to contact the manufacturer directly if they wanted further information on the suitability of a product (Coeliac UK, 2016b).

Behavioural modification

"Your View" identified certain issues which were barriers faced by CD patients on a daily basis and preventing them from following a GFD. The modifiable issues included external environmental stimuli; different sets of stimuli were identified for Caucasians and South Asians. Topic discussed were: eating out, receiving guests, anxiety about the long-term effects of a GFD, personal privacy about the diagnosis, the taste of GF foods and associated costs of a GFD. Before engaging patients in the behavioural discussion, they were asked about their position on the behavioural spectrum of the Trans-theoretical stages of change model (Appendix 1.3J). Linked with the leaflet, they were specifically asked about their challenges and given specific advice/ counselling about adherence to a GFD in such situations.

Eating out:

Clear information was given to the patients on individual matters and guidance was drawn from Coeliac UK on eating out (Coeliac UK, 2016a). They were informed that caterers must, by law, be able to provide you with information on any allergens, including cereals containing gluten, in all the dishes they serve (picture No 10). This means that if a recipe uses cereals containing gluten (such as wheat, rye, barley or oats), they will have provide this information. However, although caterers have to provide allergen information for all of the dishes they serve, they don't have to offer a GF meal, so it is best to call ahead or check their website to see if they offer gluten free options. Patients were advised that they could speak to restaurant staff and explain why they needed to avoid any foods that contained gluten. They could highlight what foods are naturally gluten free and suitable to eat; provide specific examples of what is not safe e.g. wheat flour in sauces, breadcrumbs, croutons, some stock cubes/powders and oil previously used to fry foods that contain gluten. If an ingredient is bought-in, such as stock cubes, restaurant staff, can check the ingredients list as they are covered by the same EU wide labelling laws as foods in the supermarket. If there is nothing suitable on the menu, patients were advised to ask if the chef could cook something else for them; many restaurant chefs are happy to do this once they know the reason for the request.

Cross Contamination*:*

To avoid cross contamination in food preparing areas, patients were advised to wipe down surfaces and clean pots and pans with soap and water. Standard washing up or using a dishwasher will also remove

gluten and washing up liquids are fine to use. Standard rinsing will remove any traces, so separate cloths or sponges are not required, although they may want to get separate bread boards to keep GF and gluten-containing breads apart. Use separate toasters or toaster bags, clean oil or a separate fryer for frying gluten free foods. Use different butter knives and jam spoons to prevent breadcrumbs from getting into condiments.

Individual modification(s)

There are several ways to enhance the counselling process, but one of the most effective tools is to communicate in the patient's language (Ferguson & Candib, 2002). Patients may be persuaded to keep "health first" or may be engaged in a dialogue where specific scenarios are reconstructed and the problem is broken down to identify the micro barriers and how to overcome them (for example by communicating in an assertive way). Patients may be asked to keep a diary of transgressions and write down key events leading to such transgressions and to avoid them if possible. Patients will be informed about SMART goals; SMART is the acronym for: Specific, Measurable, Achievable, Relevant and Time-limited (O'Neill, 2000, Monaghan et al., 2005, Playford et al., 2009). A detailed example of a SMART goal is shown below (Table No 48)

Table 48. SMART goal in relation to CD

SMART	Goal	Example
Specific	What do I want to accomplish? Why do I want to accomplish this? What are the requirements? What are the constraints?	I want to be adherent to a GFD. The requirement is to avoid gluten products altogether and it involves changing lifestyle and eating habits.
Measurable	How will I measure my progress? How will I know when the goal is accomplished?	Maintain a food diary which shows that gluten products have not been consumed.
Achievable	How can the goal be accomplished? What are the logical steps I should take?	In order to accomplish this goal I must avoid situations which leads to transgressions.
Relevant	Is this a worthwhile goal? • Is this the right time? • Do I have the necessary resources to accomplish this goal? • Is this goal in line with my long term objectives?	It is a worthwhile goal as your short and long-term health depends on this.
Time bound	How long will it take to accomplish this goal? When is the completion of this goal due? When am I going to work on this goal?	It is an ongoing modification to your lifestyle to avoid gluten.

Specific issues

Asymptomatic Individuals

The asymptomatic patients were approached very carefully and their beliefs about the activity and potential complications of coeliac disease were explored. After confirming that they were diagnosed on histological grounds, they were given a detailed illustration about the inflammatory aspect of CD (explained below). They were then given a detailed overview about the role of exposure to dietary antigens and the ongoing inflammation despite lack of symptoms. Personal privacy about the diagnosis was acknowledged to be a difficult area.

Follow up

Patients were followed up after 3 months with a postal questionnaire (Leffler 2009) to measure adherence and a CD quality of life questionnaire. A change in circumstances form (Appendix 1.3J) was sent at each follow up to keep in view the significant variables which may potentially affect the adherence CDQoL questionnaire (Crocker et al., 2013). The details of intervention and follow up are given in the table below (Table No 49).

Table 49 Details of questionnaires used in the intervention and the target groups

	Non-Adherent	**Adherent**
Timeline	**Intervention**	**Non-Intervention**
Pre-intervention	CDAT DASS CD related QoL CD Knowledge Q	CDAT DASS CD related QoL CD Knowledge Q
3 months post intervention	CDAT Change in circumstances Q CD related QoL CD Knowledge Q	CDAT Change in circumstances Q CD related QoL CD Knowledge Q
6 months post intervention	CDAT Change in circumstances Q	CDAT Change in circumstances Q

Materials used:

A postal invitation in the form of a research pack was sent to all eligible patients (Root & Blismas, 2003). The research pack (contained in an A5 envelope) included an invitation letter (Appendix 1), patient information sheet, study questionnaire, consent form and details for completing the study questionnaires, along with a stamped addressed envelope (Appendices 1.3 A-E). Demographic data was collated from the CD database of DGH; adherence and quality of life related questions were extracted from the questionnaire.

Instruments used

A detailed overview of the general aspects of questionnaire selection has been provided elsewhere (Study I, pages 40 to 47) and will not be repeated here. Additionally, the CDAT questionnaire, which was part of study I, has also been explained in the relevant section and will not be repeated here. New questionnaires used in this research study include: Depression Anxiety Stress Score (DASS) (Henry & Crawford, 2005), GFD scale by Silvester and colleagues (Silvester et al., 2016), Coeliac Disease Quality of Life (CDQoL) questionnaire (Crocker et al., 2018a, Crocker et al., 2018b) and Change in Circumstances (CIC) questionnaire; these are explained below.

DASS-21 Questionnaire

Each participant received the DASS-21 questionnaire: a one page short questionnaire (Lovibond & Lovibond, 1995) which is a purpose built instrument for the assessment of three negative emotional states of mental health i.e. depression, anxiety and stress. It is an abridged version of the DASS-42, a self-report instrument also designed to measure the above three negative emotional states. It is divided into three sections, each representing the above elements and each has seven questions and each question had four possible answers to choose from (did not apply to me at all; applied to me to some degree, or some of the time; applied to me to a considerable degree, or a good part of time; applied to me very much, or most of the time). Based on the scoring system, each element of mental health is then identified as normal, mild, moderate, severe or extremely severe. For depression, for example, a score of five and above reflects mild depression and a score of 14 and above is suggestive of severe depression. The table below (Table No 50) shows the scoring system from DASS-21 for different elements and the form is attached as appendix 1.3G.

Table 50: Elements of DASS-21 score and calculations of severity of individual elements

	Elements of mental health		
	Depression	**Anxiety**	**Stress**
Severity			
Normal	0-4	0-3	0-7
Mild	5-6	4-5	8-9
Moderate	7-10	6-7	10-12
Severe	11-13	8-9	13-16
Extremely severe	14+	10+	17+

Silvester Gluten-Free Diet Knowledge Scale

This GF diet knowledge questionnaire was received by participants both at baseline and then at month three and was divided into three kinds of food items, namely: allowed, to question and not allowed. The participants answered them in two ways; they identified the food item in the correct category and based on this were either wrong or right in their selected option. The knowledge questionnaire was, thus, analysed twice: once to check if they had answered the questions at base line correctly and then to see if they could identify the item in the correct category. This was done to simplify future analysis of improvement or decrement in CD knowledge. The overall GFD knowledge was the cumulative score from individual choices and ranged from 0-17, with 17 the most knowledgeable in relation to a GFD.

The types of foods referred to in the questionnaire included those which could be consumed on their own and those which might be used in the preparation of another product. There were 17 different food items: seven each in the “allowed” and the “to question” categories and three in the ”not allowed” category. This identified two types of patients: those who were over-restricting themselves by avoiding allowed food items (thinking that they were not allowed) and those who were erroneously eating food items which were not allowed. The details of the questionnaire are available in the appendix 1.3F.

Change in Circumstances form

This was a short questionnaire which explored changes in several aspects of a patient's life which may affect their adherence, as shown by previous research, thus serving as a confounder (Appendix 13J). The most important of them was membership of Coeliac UK (Muhammad et al., 2017) and this was the first question, with two possible answers ("I am a member of Coeliac UK" or "I am no longer a member of Coeliac UK"). This was followed by doctor or dietitian appointment to see if they had an appointment with a doctor/ dietitian and again this had two choices i.e. yes or no. Next, the buying capacity of GFP was explored and it had three choices which were: I can afford all, some or none of the GFP. Next, patients were asked if they had developed an allergy to GFP, as that may potentially affect adherence. Then their mental health was explored, as one of the exclusion criteria was a diagnosis of depression (which may decrease adherence to a GFD). Similarly, a diagnosis of anxiety was explored, as it was also one of the exclusion criteria (Appendix 1.3J).

Coeliac Disease Quality of Life (CDQoL) Questionnaire

The Coeliac Disease Quality of Life CDQoL is a 32 item validated instrument addressing five dimensions: stigma (8 items); dietary burden (8 items); symptoms (5 items); social isolation (5 items); worries and concerns (6 items) (Appendix No 1.3H). The questionnaire measures Health Related Quality of Life (HRQoL) over the preceding four weeks. The CDQoL was developed by researchers within the Health Services Research Unit, part of the Nuffield Department of Population Health at the University of Oxford; a license was formally granted for the use of this questionnaire in the study. Dimension scores and an overall index score can be calculated for the CDQoL. Raw scores are transformed to a 0-100 scale, where 0 is the poorest quality of life and 100 is the highest quality of life. Details of the scoring system for the CDQoL, along with the questionnaire, are attached as appendix 1.3 H&I.

Study management

Ethics

The Integrated Research Application System (IRAS) was used to apply for ethical approval for the study (IRAS ID: 214859). The study was first approved by Roehampton University Ethics Committee (email dated 19/07/2017, LCS 16/190). Thereafter, ethical approval was applied for through the central Research and Ethics Committee (REC) and permission was granted from the REC NHS Leicester Central (Ref: 17/EM/00 56). This was further approved by HRA (letter attached 21st April, 2017 Appendix No 2.3B); finally the local NHS research and development department at DGH was involved through a site specific application form linked to the IRAS form and approval was granted (email dated 12th May). The study applied for registration on a public data base as per the requirement of HRA and the Universal Trial reference Number (UTIN) for this trial is U1111-1226-9074 (Appendices No 2.3A-D)

Procedure

Each participant was given a unique trial number, which was assigned by the principal investigator to preserve the confidentiality of the patients. Assurance regarding the confidentiality was clearly stated in the invitation letter and patients were encouraged to clarify any concerns by either writing to the researchers or telephoning them on a particular day (Wednesday afternoons). Contact details for the acquisition of independent information were also provided. There was a separate section at the end of the questionnaire which the patients could sign and return to acknowledge receipt and which also gave them the opportunity to request not to be contacted for such studies in the future.

During the recruitment phase of the study, extreme care was taken to preserve the confidentiality of the patients by constructing a comprehensive password protected database. The database was received from the dietitian department using the NHS Trust's email and only Trust specified memory sticks were used. Data was accessed on a need only basis. The researcher analysed the diagnostic database and only relevant details (like age, sex, ethnicity, basic information given at the first meeting with the dietitian and histological confirmation) were entered into the database. Only then were the questionnaires sent out.

The first phase of the study was the postal recruitment phase, where patients were identified by their pre-allocated number. The suitably identified patients were carefully re-evaluated prior to sending out

the research pack. This was a precautionary measure to ensure compliance with the exclusion criteria and prevent any unintended recipients receiving the pack (e.g. minors or deceased patients). Additional information gained from the CD database (like age, ethnicity and gender) was also entered onto the already generated research database.

The returned questionnaire was kept in a separate file in the research room of DGH and all identifiable data was kept linked only to trial number to protect confidentiality. Each response on the questionnaire was coded from 0 to 5. The following information was entered into the database: gender, age and ethnicity (1- 4). Once this round was completed, the data was analysed according to the statistics section below. For complex statistical analysis, including logistic regression, data with multiple factors was split into subsections, each with a value of 0 or 1, signifying absence or presence of the concerned factor respectively.

Data management

Data Entry:

In the first stage, the entered data was checked for any errors and missing data. The researcher found four cases where typographical errors were detected and a further two cases where the data was missing. Missing data was cross checked with the paper based collected data and the missing values were rectified. Following this, in the second stage, coding of the data was cross verified and no coding errors were identified. All entries in the software were done by the researcher (author) and no omission in the data was left. It was planned to spot missing data and to complete it with terms like ND (not done), NA (not applicable), NK (not known). Ambiguous phrases such as ‘not available’ were avoided. No patients withdrew from the study, although it was made clear to the patients that they were allowed to withdraw from the study at any time without being questioned about the reasons.

Data Analysis:

Data was entered and analysed using SPSS V 24 (IBM SPSS Inc., Chicago, IL). Data was initially evaluated for characterization of the recruitment cohort; age range, gender distribution, ethnic variation and evidence for diagnosis were also explored. To detect skewness, continuous variables e.g. age, were screened for normal distribution by using the Kolmogorov-Smirnov test. In addition to χ^2 test other nonparametric tests such as Mann-Whitney U (MWU), Wilcoxon signed-rank and Kruskal-Wallis tests

were used to compare percentages. 2X2 contingency tables were used to compare nominal data in cross tabulation. Odds Ratio (OR) was calculated for the table Student's t-test or equivalent non parametric tests were used to analyse the difference between mean age and length of follow-up since diagnosis of the returnees and non-returnees of the questionnaire among the Caucasian and South Asian patients. Additionally, binary Logistic Regression was used to find association between certain parameters (membership of Coeliac Society, understanding food labels etc.) and adherence with a GFD. Logistic Regression analysis provided *p* values and an OR with 95% confidence interval. For the purpose of this test and the study, all statistical values with a *p* value of <0.05 were considered significant.

SECTION II

Results

Study population:

The Dietetic department database generated 213 patients, out of which 195 were selected for the postal invitation and 18 patients were excluded (based on the exclusion criteria). Out of the excluded patients, eight patients were below the age of 18 and one was a duplication of data. A further four patients were excluded as they had died by the time the data was being analysed for inclusion into the study, based on the current information available from the mortality database of the hospital. There was no contact address for the five remaining excluded patients; they were assumed to have moved out of the area or changed their address but not updated it on the system. After the Intervention, at the time the study was being written, the local clinical commissioning group (in accordance with national guidelines) had also published new guidelines on their website regarding restricting certain gluten free products on prescription (CCG Dudley, 2018).

Age, ethnicity and gender of the study population:

The 195 patients consisted of 57 (29.2%) males and 138 (70.8%) females and there were 170 (87%) White Caucasians out of which 122 (62%) were females and the remaining were males. There were 16 (8.2%) South Asian females in the sample. The ages of the population ranged from 18 to 70 years (M = 50.6, SD = 52). Age was non-normally distributed (p=0.00), with skewness of -0.82 (SE = 1.35) and kurtosis of -1.14 (SE = .364). There was a significant difference between the ages of males (Mdn = 57, n = 57) and females (Mdn = 49, n = 138), U = 3016, z = -2.55, p = .01, r = -.18. The result thus shows that the sample was White Caucasian female predominant and females were significantly older than males. (Appendices 4.3A a-d)

Responders and non-responders of the invitation to participate.

Out of 195 postal invitations, 125 completed questionnaires were received, which gives a return (completion) rate of 64% and this was achieved in phases by sending reminders (Tai et al., 1997, Silva et al., 2002). In addition, four other responses were received marked “returned to sender” and no further attempt was made to contact them, as it was assumed that they had moved. None of the questionnaires

had missing data and the information was legible. The table below shows the characteristics of the responding and non-responding populations. (Table No 51)

Table 51: Characteristics of responders and non-responders to invitation to participate.

Variables	Total	Response status		*P* Value
		Responders	Non-Responders	
	195	125 (64.1%)	70 (35.8%)	
Median Age (IQR)	52 (33-67)	51 (33-67)	53 (31-69)	0.82*
Age Groups				
< 20 years	7 (3.3%)	3 (2.4%)	4 (5.7%)	
21-30 years	31 (15.9%)	19 (15.2%)	12(17.1%)	
30-40 years	26 (13.3%)	17(13.6%)	9 (12.9%)	
41-50 years	27 (13.8%)	20 (16%)	7 (10%)	
51-60 years	36 (18.5%)	25 (20%)	11 (15.7%)	
61-70 years	32 (16.4%)	20 (16%)	12 (17.1%)	
> 70 years	36 (18.5%)	21 (16.8%)	15 (21.4%)	
Gender				.24**
Male	57 (29.2%)	33 (26.4%)	24 (34.3%)	
Female	138 (70.7%)	92 (73.6%)	46 (65.7 %)	
Ethnicity				.18**
White Caucasians	170 (87.2%)	106 (84.4%)	64 (91.4%)	
South Asians	25 (12.8%)	19 (15.2%)	6 (8.6%)	

IQR: Inter Quartile Range, *MWUT, ** χ2 test.

The ages of the responders ranged from 18 to 83 years (Mdn = 51, IQR 33-67) and were not distributed normally (p<0.001), with skewness of -.085 (SE = -.217) and kurtosis of -1.07 (SE = .43). The ages of those who did not return the questionnaire ranged from 18 to 87 years (Mdn = 53, IQR 31-69). Similarly, they were not distributed normally (p=.00), with skewness of -.092 (SE = .28) and kurtosis of -1.29 (SE = .56). A Mann-Whitney U test did not find any significant difference in the ages of responders (Mdn = 51, n = 125) and non-responders (Mdn = 53, n = 70), U = 4293, z = -216, p = .829, r = 0.01.

Correspondingly, a chi-square for independence indicated no significant difference between gender and questionnaire return rate, $\chi 2$ (1, n=195) = 1.35, p=0.24, phi = -.083. Likewise, there was no significant association between ethnicity and questionnaire return rate, $\chi 2$ (1, n=195) =1.76, p=0.18, phi = -.095. (Appendices 4.3Ba-d)

Depression Anxiety and Stress Score (DASS)

Severe depression was one of the exclusion criteria and patients were asked to fill in the DASS-21 (Henry & Crawford, 2005) questionnaire to assess their depression, anxiety and stress scores. A total of 87 (44.6%) completed DASS questionnaires were received, which is a sub-set of the 125 responders; none of the patients had severe depression, although one patient was found to have severe anxiety. The DASS depression scores ranged from 4 to 15 (M = 8.6, SD = 2.1) and were non-normally distributed (p=<0.01), with skewness of .45 (SE = .26) and kurtosis of .38 (SE = .53). Similarly, the DASS anxiety scores ranged from 4 to 15 (M = 8.6, SD = 2.1) and were non-normally distributed (p<0.01), with skewness of .45 (SE = .26) and kurtosis of .38 (SE = .53). Likewise, the DASS stress scores ranged from 4 to 15 (M = 8.6, SD = 2.1) and were non-normally distributed (p<0.01), with skewness of .45 (SE = .26) and kurtosis of .38 (SE = .53). The table below shows the relative scores of the different categories in comparison to the total scores (Table No 52).

Table 52: Results of the DASS 21 questionnaire

	Total	**Gender**						
		Male			Female			
	N= 87	N= 25			N= 62			
Variable	Median (IQR)	Median (IQR)	Min	Max	Median (IQR)	Min	Max	P*
Age	51 (33-67)	57 (43-72)	18	83	48 (32-62)	18	87	.05
DASS total depression score	9 (7-10)	8 (7-9)	5	13	9 (7-10)	4	15	.35
DASS total anxiety score	8 (6-9)	8 (6-9)	4	16	8 (6-9)	3	20	.73
DASS total stress score	9 (7-12)	9 (6-15)	2	21	9 (6-12)	3	21	.85

***MWUT**

DASS questionnaire analysis showed that males (Mdn = 56, n = 25) were significantly older than females (Mdn = 48, n = 62), U = 569, z = -1.93, p = .05, r = .20, but there was no significant difference between genders in relation to depression; U = 677, z = -.93, p = .35, r = .1, anxiety U = 1064, z = -.34, p = .73, r = .03 or stress U = 1080, z = -.18, p = .85, r = .01, which means that neither gender was excessively depressed, stressed or anxious as compared to the other gender.

Based on their DASS score, each individual was classified as depressed or not depressed; if depressed, they were then sub categorised as: mild, moderate, severe or extremely severe. Depression was found in 26 (20%) of the patients but was generally mild (n=25) and none of the patients was severely depressed (which was one of the exclusion criteria). The table below shows the results of the DASS questionnaire (Table No 53) (Appendices 4.3Ca-g).

Table 53: Results of the DASS questionnaire

		Gender		Total	
		Male (n=25)	Female (n=62)	n=87	X^2 (p)
Depression					1.8 (.40)
	None	20 (80%)	41 (66.1%)	61 (70.1%)	
	Mild	5 (20%)	20 (32.3%)	25 (28.7%)	
	Moderate	--	1 (1.6%)	1 (1.1%)	
	Severe	--	--	--	
	Extremely severe	--	--	--	
Anxiety					1.34 (.85)
	None	10 (40%)	25 (40.3%)	35 (40.2%)	
	Mild	11 (44%)	23 (37.1%)	34 (39.1%)	
	Moderate	1 (4%)	6 (9.7%)	7 (8.0%)	
	Severe	3 (12%)	7 (11.3%)	10 (11.5%)	
	Extremely severe	--	1 (1.6%)	1 (1.1%)	
Stress					2.60 (.45)
	None	19 (76%)	54 (87.1%)	73 (83.9%)	
	Mild	5 (20%)	6 (9.7%)	11 (12.6%)	
	Moderate	1 (4%)	1 (1.6%)	1 (1.1%)	
	Severe	--	1 (1.6%)	1 (1.1%)	
	Extremely severe	--	--	--	

Further analysis indicated that none of the DASS components were significantly different between genders. It is thus concluded that, although there was some degree of depression among patients, no cases were considered severe enough to require exclusion from the study (Appendices 4.3Ca-g).

SECTION III

Baseline or Pre Intervention Data

Leffler Questionnaire

All patients (n=125) who returned the questionnaires completed the Leffler questionnaire and none of the data was left blank. CDAT score was calculated from the cumulative scores of individual components and based on that patients were divided into two groups: adherent to GFD (CDAT <13) and non-adherent to GFD (CDAT>13) (Leffler et al., 2009). The adherent group will be termed the control group from now onwards and the non-adherent group will be called the intervention group. CDAT scores for the entire population (n=125) ranged from 7 to 20 (Mdn = 10, IQR= 9-12) and were not distributed normally ($p<0.01$), with skewness of 1.06 (SE = .217) and kurtosis of .41 (SE = .43). The bar chart below shows the CDAT scores of the entire population of responders (Fig No 33) (Appendix 4.3da)

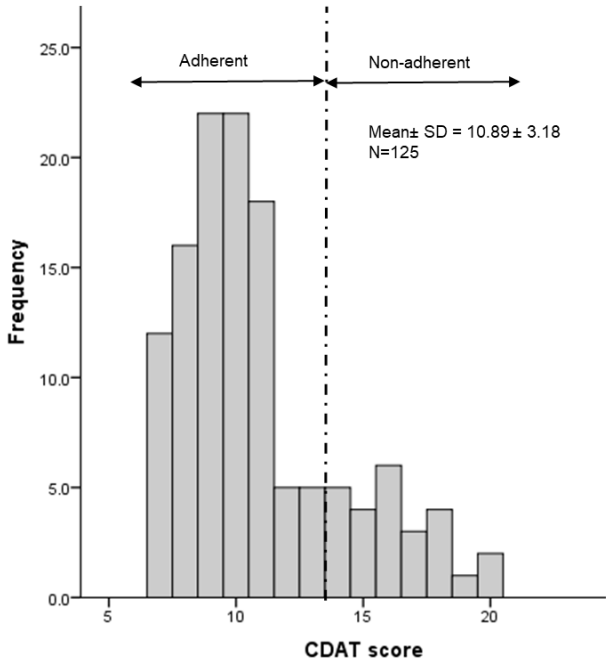

Figure 33: CDAT scores of the study population (n=125). Dotted line shows the cut-off point of for the adherent group (to the left CDAT score <13), with the non-adherent group to the right.

The most prevalent scores were 9 and 10 (n=22) followed by 11 (n=18). 30 participants (24%) were therefore in the intervention group and the remaining (n=95) were in the control group. There were 15% (n=19) South Asians in the cohort and all of them had a score <13, thus indicating adherence to a GFD.

Age, Gender and Ethnicity in relation to CDAT score (Baseline):

There was no significant difference between the CDAT scores of both genders. CDAT scores for males ranged from 7 to 18 (Mdn = 10, IQR= 9-12) and were not distributed normally (p<0.01), with skewness of .89 (SE = .40) and kurtosis of .13 (SE = .79). Likewise, CDAT scores of female ranged from 7 to 20 (Mdn = 10, IQR= 9-12) and were not distributed normally (p<0.01), with skewness of .897 (SE = .4) and kurtosis of .136 (SE = .798). A Mann-Whitney U test indicated no significant difference in the CDAT scores for males (Mdn = 10, n =33) and females (Mdn = 10, n = 92), U = 1458, z = -.336, p = 0.737, r = -0.03 (Appendix 4.3Da).

Participants with white ethnicity had significantly higher CDAT scores compared with South Asian participants, suggesting lower adherence to a GFD. CDAT scores for those of white ethnicity ranged from 7 to 20 (Mdn = 10, IQR= 9-13) and were not distributed normally (p<0.01), with skewness of .893 (SE = -.23) and kurtosis of -.03 (SE = .46). However, CDAT scores of South Asians ranged from 7 to 12 (Mdn = 9, IQR= 8-10) and were distributed normally (M = 9.1, SD = 1.39) (p=.14), with skewness of .26 (SE = .52) and kurtosis of -.24 (SE = 1.01). A Mann-Whitney U test revealed a significant difference in the CDAT scores for white ethnicity (Mdn = 10, n =106) and South Asians (Mdn = 9, n = 19), U = 627, z = -2.63, p <0.01, r = -0.23 (Appendix 4.3Db).

CDAT score was a combination of several statements categorised as: symptoms, social, psychological and gluten exposure. The most prevalent answer was low energy (70%), followed by report of difficulties while dining out (69%). Similarly the mean score for low energy was the highest (1.9), followed by difficulties dining out. The mean score for those who ate gluten on purpose was 1 and this was the lowest. None of the data was distributed normally as both Kolmogrove-Smirnove (KS) and Shapiro-Wilk (SW) tests had significant p values (p<0.001). The results of median scores along with IQR of individual components of CDAT are shown in the table below (Table No 54).

Table 54: Comparing CDAT scores of the responders at baseline based on gender and ethnicity

			Gender					Ethnicity				
	Total (N=33)		Male (N=234)		Female (N=92)			White (N=106)		Asians (N=19)		
	Median (IQR)	Min-Max	Median (IQR)	Min-Max	Median (IQR)	Min-Max	*P**	Median (IQR)	Min-Max	Median (IQR)	Min-Max	*P**
Statements in CDAT Score												
Symptoms of CD												
Low energy	2 (1-3)	1-5	1 (1-3)	1-5	2 (1-3)	1-5	.84	2 (1-3)	1-5	1 (1-2)	1-4	**.01**
Headache	1 (1-2)	1-4	1 (1-2)	1-4	1 (1-2)	1-4	.06	1 (1-2)	1-4	1 (1-2)	1-2	.29
Social Issue												
Follow GFD while dining out	2 (1-2)	1-4	2 (1-2)	1-4	2 (1-2)	1-4	.88	2 (1-2)	1-4	1 (1-1)	1-3	**.00**
Psychological												
Consider the consequences	1 (1-2)	1-4	1 (1-2)	1-3	1 (1-2)	1-4	.35	1 (1-2)	1-4	1 (1-2)	1-3	.93
Don't consider myself a failure	1 (1-2)	1-5	1 (1-2)	1-4	1 (1-2)	1-5	.99	1 (1-2)	1-5	1 (1-2)	1-2	.68
Gluten Exposure												
Accidental gluten exposures	1 (1-2)	1-5	1 (1-2)	1-5	1 (1-2)	1-5	.77	1 (1-2)	1-5	1 (1-2)	1-2	.19
Eaten gluten on purpose	1 (1-1)	1-3	1 (1-1)	1-2	1 (1-1)	1-3	.41	1 (1-1)	1-3	1 (1-1)	1-1	.12
Overall CDAT score	10 (9-12)	7-20	10 (9-12)	7-18	10 (9-13)	7-20	.73	10 (9-12)	7-20	9 (8-10)	7-12	**.00**

***MWUT**

It is evident from the table above that South Asian participants had significantly better GF dietary adherence scores compared with White Caucasians, whilst there was no difference in component CDAT scores between the two genders. When the Leffler questionnaire was analysed for detecting adherence based on the frequency of knowingly ingesting gluten (statement no 7), the results showed that the GF dietary adherence rate was 90.4% and the majority of the patients (n=113) reported not ingesting gluten. The 12 (9.6%) patients who reported ingesting gluten in some form were either ingesting on a monthly (n=10) or weekly basis (n=2) and none of the patients reported ingesting gluten on a daily basis. This distinction is important in relation to the presentation of the remaining results, as non-adherence in this study is based on the validated CDAT score of > 13 and not on the frequency of knowingly ingesting gluten (Appendix 4.3Da-g).

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Demographics and CDAT scores of the study groups at base line

The ages of those in the intervention group ranged from 18 to 87 (Mdn = 52, IQR = 34-59) and were not distributed normally (p<0.01), with skewness of -.082 (SE = .42) and kurtosis of -1.37 (SE = .83). The ages of females (n=23) in this group ranged from 21 to 73 (M = 48.5, SD = 18.5), normally distributed (p=.20), with skewness of .037 (SE = .48) and kurtosis of -1.56 (SE = .481). MWU test did fnot detect a significant difference between the ages of intervention (Mdn=53, n=30) and control (Mdn=51, n=95), U = 1374.5, z = -2.9, p=0.77, r = -0.24 (Appendix 4.3Eb). Furthermore, the ages of males in this group (n=23) ranged from 39 to 81 (M = 59.7, SD = 15.6). Similarly, they were normally distributed (p=.20), with skewness of -.056 (SE = .794) and kurtosis of -1.37 (SE = 1.58) and there was no significant difference between the ages of males (M = 59.7, SD = 15.6) and females (M = 48.5, SD = 18.5) conditions; t (28) =1.44, p =0.16 (Appendix 4.3Eg)

In the control group, there were 95 (76%) patients who were adherent to a GFD and this group was predominantly composed of females (77%) and of white ethnicity (76%). Additionally, the ages of those in the control group ranged from 18 to 83 (Mdn = 51, IQR = 33-64) and were non-normally distributed (p<0.01), with skewness of -.088 (SE = .24) and kurtosis of -.97 (SE = .49). In addition to that, the ages of females (n=69) in this group ranged from 18 to 82 (Mdn = 49, IQR = 32-47) and were not distributed normally (p<0.01), with skewness of .065 (SE = .89) and kurtosis of -.83 (SE = .57). Furthermore, the ages of males in this group (n=26) ranged from 19 to 83 (Mdn = 57, IQR = 44-71) and were non-normally distributed (p<0.01), with skewness of -.56 (SE = .456) and kurtosis of -.72 (SE = .88). The table below compares the intervention and control groups (Table No 55).

Table 55: Characteristics of intervention and control groups

Variables	N (Total)	Study Groups		Significance
		Intervention	Control	
	125	30	95	
Median Age (IQR)	51 (33-67)	52 (34-69)	51 (33-64)	U =1374, P= .77
Age Groups				X^2= 4.9, P=.54
< 20 years	3 (2.4%)	0 (0%)	3 (2.4%)	
21-30 years	19 (15.2%)	5 (4.0%)	14 (11.2%)	
30-40 years	17(13.6%)	6 (4.8%)	11 (8.8%)	
41-50 years	20 (16%)	3 (2.4%)	17 (13.6%)	
51-60 years	25 (20%)	4 (3.2%)	21 (16.8%)	
61-70 years	20 (16%)	5 (4.0%)	15 (12.0%)	
> 70 years	21 (16.8%)	7 (5.6%)	14 (11.2%)	
Gender				X^2= .191, P=.66
Male	33 (26.4%)	7 (5.6%)	26 (20.8%)	
Female	92 (73.6%)	23 (18.4%)	69 (55.2%)	
Ethnicity				**X^2=7.07, P.00**
White Caucasians	106 (84.8%)	30 (100%)	76 (80%)	
South Asians	19 (15.2%)	0 (0%)	19 (20%)	

IQR: Interquartile range

It is clear from the table above that there was no difference between the ages of patients in the intervention and control groups. Similarly, there was no difference between the age groups and gender distribution, however the intervention group was entirely composed of White Caucasians (Appendix 4.3b-h).

CDAT scores (n=125) ranged from 7 to 20 (Mdn = 10, IQR 9-12) and were not distributed normally (p<0.01), with skewness of 1.06 (SE = .21) and kurtosis of -.41 (SE = .43). CDAT scores for the intervention group ranged from 13 to 20 (M = 15.7, SD = 2.0) and were normally distributed (p=.18), with skewness of .40 (SE = .42) and kurtosis of -.69 (SE = .83). In contrast the CDAT scores for the control group (n=95) ranged from 7 to 12 (Mdn = 9, IQR 8-10) and were not distributed normally (p<0.01), with skewness of -.054 (SE = .24) and kurtosis of -.90 (SE = .49).

The intervention group had significantly higher median CDAT scores as compared to the control group; a Mann-Whitney U test revealed a significant difference in the CDAT scores for the intervention (Mdn = 16, n =30) and control groups (Mdn = 9, n = 95), U = .00, z = -8.33, p = .00, r = -0.75. The bar chart below shows the comparison of the groups (Fig No 34) (Appendix 4.3Ek)

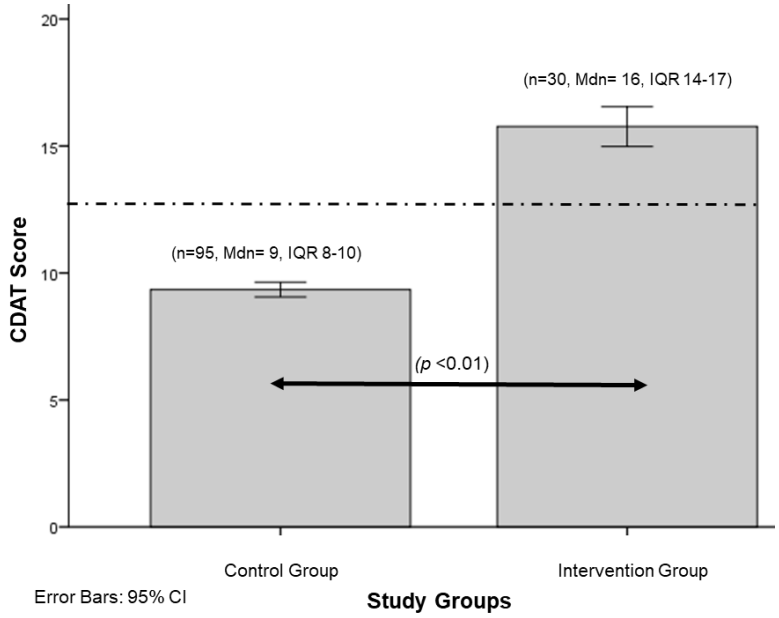

Figure 34: Comparison of CDAT scores of both groups. Dotted line shows the cut-off point for adherence (below the line CDAT score <13). Mdn= median, IQR= inter quartile range.

Different components of the CDAT scores were analysed; significance was calculated by the MWU test and is presented in the table below (Table No 56).

Table 56: Comparison of CDAT scores between intervention and control groups

		Study Groups				
Statements in CDAT Score	**Total (n=125)**	**Intervention Group (n=30)**		**Control Group (n=95)**		
Symptoms of CD	Mdn (IQR)	Mdn (IQR)	Min-Max	Mdn (IQR)	Min-Max	***P****
Low energy	2 (1-3)	3 (2-3)	1-5	1 (1-2)	1-5	**<0.01**
Headache	1 (1-2)	3 (2-3)	1-4	1 (1-2)	1-4	**<0.01**
Social Issue						
GFD while dining out	2 (1-2)	2 (2-3)	1-4	1 (1-2)	1-3	**<0.01**
Psychological						
Consider the consequences	1 (1-2)	1 (1-2)	1-4	1 (1-2)	1-3	**.01**
Don't consider myself a failure	1 (1-2)	1.7 (2-3)	1-3	1 (1-2)	1-5	**<0.01**
Gluten Exposure						
Accidental gluten exposures	1 (1-2)	3 (2-4)	1-5	1 (1-1)	1-3	**<0.01**
Eaten gluten on purpose	1 (1-1)	1 (1-2)	1-3	1 (1-1)	1-2	**<0.01**
Overall CDAT score	10 (9-12)	16 (14-17)	13-20	9 (8-10)	7-12	**<0.01**

IQR= Interquartile range, *MWU test

Higher median values were observed for the majority of subgroups in the intervention group compared with the control group. The increase in CDAT score (>13) was not limited to one component of the CDAT score: rather, it was significantly present in all statements (Appendices 4.3Eo).

CD knowledge of the study groups at base line

A total of 116 (92.8% of the 125) completed knowledge questionnaires (Silvester et al., 2016) were received at baseline. Silvester scores ranged from 10 to 17 (Mdn = 15, IQR = 14-16) and were non-normally distributed (p<0.01), with skewness of -.54 (SE = .22) and kurtosis of .16 (SE = .44). For males (n=30) the scores ranged from 10 to 17 (Mdn = 14.5, IQR = 14-16) and were non-normally distributed (p<0.01), with skewness of -.90 (SE = .42) and kurtosis of .09 (SE = .64). Similarly, for females (n=86) they ranged from 10 to 17 (Mdn = 15, IQR = 13-16) and were non-normally distributed (p<0.01), with skewness of -.41 (SE = .26) and kurtosis of .25 (SE = .59). A Mann-Whitney U test did not reveal a significant difference in the Silvester scores for males (Mdn = 14.5, n =30) and females (Mdn = 15, n = 86), U = 1287.5, z = -.016, p = .98, r = -0.00. The results suggest that there was no significant difference in CD knowledge between males and females in the study population (Appendix 4.3Fe). Comparing the CD related knowledge between the study groups, the total score for intervention group patients ranged from 10 to 16 (M = 13.2, SD = 1.4) and was not distributed normally (p<0.01), with skewness of -.42 (SE = .42) and kurtosis of -.44 (SE = .83). Similarly, for the control group it ranged from 10 to 17 (M = 14.9, SD = 1.3) and was also not distributed normally (p<0.01), with skewness of -.59 (SE = .26) and kurtosis of .64 (SE = .51). The bar chart below compares the scores for the groups (Fig No 35).

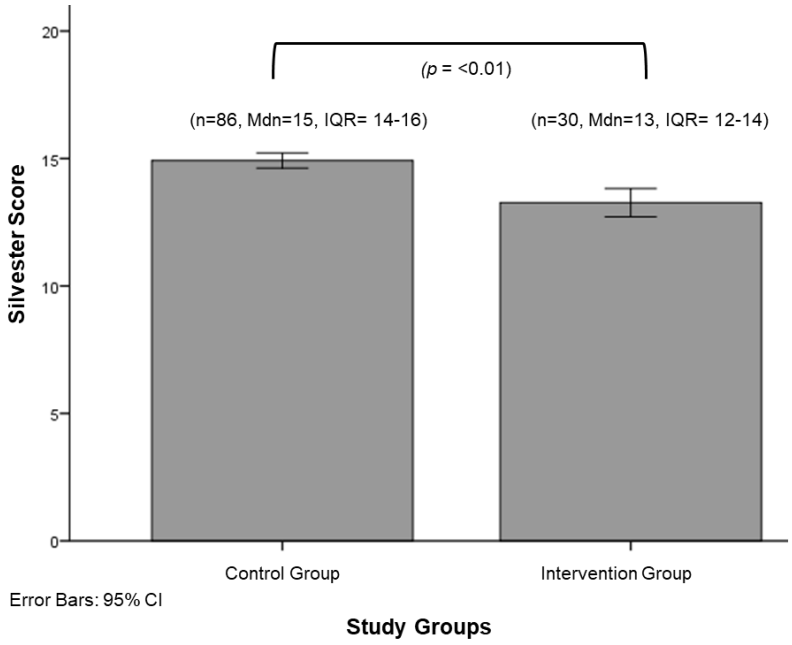

Figure 35: Comparison of Silvester scores of the intervention and control groups at baseline. IQR: Interquartile range.

A Mann-Whitney U test revealed a significant difference in the knowledge scores between intervention (Mdn = 13.5, n =30) and control groups (Mdn = 15, n = 86), U = 545, z = -4.79, p = .00, r = -0.00. At base line the control group had significantly better knowledge about CD (Appendix 4.3Fj).

Following this, individual sections of the questionnaire were analysed to see patients' knowledge about specific components of the questionnaire. The majority of participants (84-97%) were able to correctly allocate food items to their respectively categories ("allowed", "to question" or "not allowed"). Egg noodles were most often placed in the correct category (93%), followed by soy sauce (92%); whereas croutons were least often placed correctly (44.4%) The table below shows the frequency with which food items were placed in the correct category or otherwise (Table No 57) (Appendices 4.3F-cj).

Table 57: Silvester CD questionnaire in relation to identifying category

Food items	Correct identification of category			Correctly answered				
	Allowed	To question	Not allowed	Control group (n=86)		Intervention group (n=30)		P*
Allowed	n (%)	n (%)	n (%)	**n**	**%**	**n**	**%**	
Milk	**97 (83.6)**	10 (8.6)	3 (2.6)	76	88.4	26	86.7	.80
Chickpea flour	**98 (84.5)**	8 (6.9)	4 (3.4)	77	89.5	26	86.7	.66
Balsamic vinegar	**94 (81.0)**	12 (10.3)	4 (3.4)	**77**	**89.5**	**22**	**73.3**	**.03**
Buckwheat	**100 (86.2)**	7 (6.0)	3 (2.6)	79	91.9	26	86.7	.40
Glutinous rice	**98 (83.6)**	7 (6.0)	5 (4.3)	**81**	**94.2**	**23**	**76.7**	**.00**
Cocoa	**98 (83.6)**	6 (5.2)	6 (5.2)	**81**	**94.2**	**21**	**70.0**	**.00**
Modified corn	**99 (85.3)**	3 (2.6)	8 (6.9)	**82**	**95.3**	**22**	**73.3**	**.00**
Mean	**97.7 (83.9)**	7.5 (6.7)	4.7 (4.0)					
To question								
Flavoured yogurt	11 (9.5)	**93 (80.2)**	6 (5.2)	74	86.0	25	83.3	.71
Sausages	9 (7.8)	**100 (86.2)**	1 (0.9)	**82**	**95.3**	**23**	**76.7**	**.00**
Soy sauce	7 (6)	**101 (87.1)**	2 (1.7)	**84**	**97.7**	**23**	**76.7**	**.00**
Oatmeal	18 (15.5)	**90 (77.6)**	2 (1.7)	70	81.4	24	80.0	.86
Rice crisps	39 (33.6)	**63 (54.3)**	8 (6.9)	**76**	**88.4**	**21**	**70.0**	**.01**
Seafood imitation	9 (7.8)	**93 (80.2)**	8 (6.9)	73	84.9	32	80.0	.53
Croutons	33 (28.4)	**51 (44.0)**	26 (22.4)	38	44.2	14	46.7	.84
Mean	18 (15.5)	**84.4 (72.8)**	7.5 (6.5)					
Not Allowed								
Malt Vinegar	10 (8.6)	5 (4.3)	**95 (81.9)**	76	88.4	25	83.3	.47
Spelt	8 (6.9)	6 (5.2)	**96 (82.8)**	76	88.4	25	83.3	.47
Egg noodles	1 (0.9)	7 (6.0)	**102 (87.9)**	80	93.0	28	93.3	.95
Mean	6.3 (5.4)	6 (5.1)	**97.6 (84.2)**					

*Chi Square test. Bold numbers in identification category are the right choices to select.

It is clear from the above table that, in the category of allowed food items, mean correct identification was 83.9%. In this category, buckwheat was correctly assigned by 86.2% of the participants, followed by modified corn (85.3%), glutinous rice (83.6%) and cocoa (83.6%). Similarly, the mean correct identification for the second category (food items to question) was 72.8% and in this category soy sauce was correctly identified by 87.1% of participants, followed by sausages (86.2%) and then flavoured yogurt (80.2%) and imitation sea food (80.2%). The final category (of not allowed food items) was correctly identified by 87.9% of the participants. It is also evident from the above table that certain food items were wrongly identified by either placing them wrongly into a category of consumption or restriction, thus inadvertently consuming or unnecessarily restricting themselves in relation to a food item. The category most affected was “to question food items” where croutons, for example, were wrongly categorised as a consumable item by 28.4% of the participants and equally 22.4% of the participants considered croutons to be a “not allowed” food item (Appendices 4.3F a-j).

CD Quality of life questionnaire (Baseline)

The CD QoL questionnaire (CDQoL) was completed and returned by 116 (93%) participants, which is a subset of the total returners (n=125) at baseline. One questionnaire was excluded as it was incomplete, thus 115 CDQoL were available for analysis. The overall CDQoL scores ranged from 29 to 90 (Mdn = 50, IQR = 46-74) and were not distributed normally (p<0.01), with skewness of .91 (SE = .22) and kurtosis of -.66 (SE = .44).

Considering CD as stigma, 10% of the participants felt that they were often misunderstood by people in relation to CD and 33% sensed that CD was often having an impact on family and friends. Similarly, 47% thought that they were always a nuisance to other people and 36.5% felt that they sometimes received unwanted attention from others. Additionally, considering GFD as dietary burden, 35% of patients felt that they were often disappointed with the taste and often felt frustrated having to plan ahead (40%) in order to find GF food (30%).

Symptoms of CD were not a major issue and the most common symptom among CD patients was bloating (29%) followed by nausea and vomiting (46.1%). Patients also reported issues with social isolation, such as always having limitations of daily activities (7%), isolation from others because of CD (23.5%), avoiding social activities (10%), avoiding eating out (30%) and feeling down (35%). There were no major worries or concerns about general health among the patients.

CD was not felt to be a major issue in relation to social isolation by almost half of the participants, as it: never affected daily activities, left patient isolated from others (54.8%) or gave them low spirits (33.9%). Similarly, patients reported that they never felt worried about anticipation of their own illness (50.4%), or illness in a family member (48.7%). Cross contamination, nonetheless, was an issue for 35.7% of the patients. The table below shows the detailed results of the CDQoL data (Table No 58 (Appendix 4.3Ga).

Table 58: Participants' choices in the CDQoL. Highest values are depicted in bold. N=125

		Always	Often	Sometimes	Rarely	Never
CD as Stigma	Making a fuss around dietary requirements	5 (4.3%)	**45 (39.1%)**	26 (22.6%)	18 (15.7%)	21 (18.3%)
	Felt misunderstood by people	--	10 (8.7%)	43 (37.4%)	12 (10.4%)	**50 (43.5%)**
	Informing people about misunderstandings	20 (17.4%)	22 (19.1%)	**48 (41.7%)**	6 (5.2%)	19 (16.5%)
	Received unwanted attention	29 (25.2%)	19 (16.5%)	**42 (36.5%)**	--	25 (21.7%)
	Impact of CD on family and friends	28 (24.3%)	**39 (33.9%)**	13 (11.3%)	8 (7.0%)	27(23.5%)
	Uncomfortable refusing unsuitable food	16 (13.9%)	**45 (39.1%)**	18 (15.7%)	14 (22.2%)	22 (19.1%)
	Nuisance to other people	**55 (47.0%)**	18 (15.7%)	8 (7.0%)	7 (6.1%)	27 (23.5%)
	Felt guilty about other people buying GFP	7 (6.1%)	22 (19.1%)	32 (27.8%)	8 (7.0%)	**46 (40.0%)**
CD as dietary burden	Frustrated about the cost of GFP	7 (6.1%)	20 (17.4%)	20 (19.1%)	8 (7.0%)	**58 (50.4%)**
	Difficulty finding suitable food	7 (6.1%)	30 (26.1%)	34 (29.6%)	1 (0.9%)	**43 (37.4%)**
	Craved food or drinks that contain gluten	17 (14.8 %)	16 (13.9%)	33 (28.7%)	15 (13%)	**34 (29.6%)**
	Disappointed with taste /texture of GFP	6 (5.2%)	**41 (35.7%)**	40 (34.8%)	9 (7.8%)	19 (16.5%)
	Felt burdened re time taken to find GFP	9 (7.8%)	**37 (32.2%)**	32 (27.8%)	9 (7.8%)	28 (24.3%)
	Difficulty finding GFP when out	1 (0.9%)	6 (5.2%)	36 (31.3%)	35 (30.4%)	**37 (32.2%)**
	Difficulty with choices of GFP	21 (18.3%)	**36 (31.3 %)**	29 (25.2 %)	5 (4.3 %)	24 (20.9%)
	Frustrated by having to plan ahead	16 (13.9%)	**46 (40.0%)**	23 (20.0%)	7 (6.1%)	23 (20%)
Symptomatic CD	Bothered by your bowel movements	6 (5.2%)	**37 (32.2%)**	32 (27.8%)	12 (10.4%)	28 (24.3%)
	Bloating in your abdomen?	**29 (25.2 %)**	25 (21.7%)	16 (13.9%)	23 (20.1%)	22(19.1%)
	Had nausea or vomiting	1 (0.9%)	**53 (46.1%)**	12 (10.4%)	--	49 (42.6%)
	Had pain that you think was caused by CD	--	10 (8.7%)	11 (9.6%)	30 (26.1%)	**64 (55.7%)**
	Had tiredness or a lack of energy	2 (1.7%)	10 (8.7%)	21 (18.3%)	29 (25.2%)	**53 (46.1%)**
Social isolation	Daily activities have been limited by CD	8 (7.0%)	37 (32.2%)	10 (8.7%)	4 (9.6%)	**56 (54.8%)**
	Felt isolated from others because of CD	27 (23.5%)	4 (3.5%)	10 (8.7%)	11 (9.6%)	**63 (54.8%)**
	Have you avoided social activities	10 (8.7%)	36 (31.3%)	21 (18.3%)	11 (9.6%)	**37 (32.2%)**
	Have you avoided going out to eat	30 (26.1%)	16 (13.9%)	**31 (27%)**	8 (7.0%)	30 (26.1%)
	Have you felt down or in low spirits	35 (30.4%)	6 (5.2%)	23 (20.0%)	12 (10.4%)	**39 (33.9%)**
Worries and concerns	Worried that you might become ill	20 (17.4%)	15 (13.0%)	18 (15.7%)	4 (3.5%)	**54 (50.4%)**
	Worried; family member may get CD	1 (0.9%)	46 (40.0%)	9 (7.8%)	3 (2.6%)	**56 (48.7%)**
	Concerns about health problems	1 (0.9%)	43 (37.4%)	10 (8.7%)	11 (9.6%)	**50 (43.5%)**
	Concerns of becoming ill when out	29 (25.2)	18 (15.7%)	**35 (30.4%)**	12 (10.4%)	21 (18.3%)
	Accidental consumption of gluten	6 (5.2%)	2 (1.7%)	14 (12.2%)	22 (19.1%)	**71 (61.7%)**
	Concerned about cross-contamination	**41 (35.7%)**	18 (15.7%)	32 (27.8%)	11 (9.6%)	13 (11.3%)

The overall CDQoL scores for males ranged from 68 to 90 (Mdn = 48.4, IQR = 79.1-87.9) and were normally distributed (*p*=0.13), with skewness of -.77 (SE = .42) and kurtosis of .09 (SE = .83). Similarly, for females CDQoL scores ranged from 29 to 66 (Mdn = 47.3, IQR = 45.6-51.2) and were normally distributed (p=.06), with skewness of .24 (SE = .26) and kurtosis of 1.8 (SE = .51). A T test revealed a significant difference in the CDQoL scores between males (M = 83.3, SD =5.6) and females (M= 48.2, SD = 5.5) conditions; t (113) =.59, p<0.01 (Appendix 4.3Gg). The CDQoL scores of the different dimensions for the intervention and control groups are given in the table below (Table No 59) (Appendix 4.3Ge).

Table 59: CDQoL scores for the different dimensions. Values are rounded to the closest whole number.

Dimensions	**Total (115)**			**Intervention (n=30)**			**Control (n=85)**			
	*Mdn (IQR)	Max	Min	*Mdn (IQR)	Max	Min	*Mdn (IQR)	Max	Min	***P****
Stigma	44 (34-66)	97	19	50 (37-58)	91	25	41 (31-67)	97	19	.23
Dietary burden	50 (41-69)	100	22	50 (41-69)	84	25	50 (41-72)	100	22	.52
Symptoms	60 (50-80)	100	30	50 (44-56)	**90**	**30**	70 (55-80)	**100**	**35**	**<0.01**
Social isolation	50 (40-75)	100	15	50 (40-74)	95	20	55 (45-77)	100	15	.48
Worries	58 (46-71)	96	21	56 (49-68)	83	21	58 (46-75)	96	25	.39
Overall	50 (46-74)	90	29	50 (49-59)	82	29	51 (46-78)	90	39	.22

***Values are rounded to the nearest whole number, ****MWU test,**

Among the dimensions, symptoms (of CD) was the main issue affecting quality of life in both groups, followed by social isolation. The only difference between the two groups which reached significance was with regards to symptoms.

SECTION IV

Telephonic Clinic:

Thirty patients were placed in the intervention group and received telephonic clinic as an intervention. The demographics of this population have been explained above. The intervention for an individual patient was tailored according to their needs e.g. lack of motivation, knowledge gaps or complex social issues in relation to the CD diagnosis or following a GFD. The mean time taken for a clinic was 49 (SD=7.2) minutes and the duration ranged from 33 to 63 minutes. The clinic was mainly patient centred i.e. lead by patients and 73% (n=22) of the patients reported an “excellent” level of satisfaction. None of the patients was dissatisfied with the clinic and only 10% (n=3) of patients were neither satisfied nor dissatisfied.

Gluten exposure was classified as either accidental or deliberate and 36.7% (n=11) of patients admitted to deliberate exposure to gluten. A variety of issues were discussed, but they were mainly divided into four sections including issues with motivation and social issues. In the former category, 70% (n=21) had some degree of mild motivational issues based on the patients’ perception, but none had severe issues; 16.7% (n=5) had no self-reported issues with motivation. On the contrary, 66.7% (n=20) had no self-reported social issues related to a GFD or the diagnosis of CD and only five had mild issues. Based on patient information gathered from the CDQoL, Silvester and CDAT questionnaires, the majority of time (presented in bold in the table above) during the clinic was devoted to a specific targeted issue for each patient. However all patients were engaged in some degree of discussion about possible gluten ingestion, covering areas including: travelling, dining at a friend’s house and cross contamination.

SECTION V

Post Intervention Data at 3 Months

At three months post intervention, 116 completed questionnaires were received from 125 patients and this gives a return (completion) rate of 92.8%. The responders from baseline and at three months are compared in the table below (Table No 60).

Table 60: Characteristics of responder population at baseline and at three months.

		Responders		
	Total	**Baseline**	**Three Months***	***p***
N (%)	195	125 (100%)	116 (92.8%)	
Variables				
Mean Age ±SD	50.6 ±18.9	50.5 ± 17.7	51.3 ± 17.6	1.0**
Study Group	_			
Intervention	--	30 (100%)	30 (100%)	
Control	--	95 (100%)	86 (90.5%)	
Gender				
Male	57 (29.2%)	33 (100%)	30 (90.9%)	
Female	138 (70.7%)	92 (100%)	86 (93.4%)	
Ethnicity				
White Caucasians	170 (87.2%)	106 (100%)	98 (92.4%)	
South Asians	25 (12.8%)	19 (100%)	18 (94.7%)	

*% in this column represents in relation to baseline **Wilcox Sign Rank test

It is clear from the table above that the drop in responders (n=9) was only noted in the control group, which dropped to 86 responders and there was a proportionally greater drop in responses from female participants.

Assessment of change in circumstances at three months:

A total of 116 patients completed the change in circumstances questionnaire, 30 (24%) of whom were in the intervention group and the remaining were in the control group. The table below shows the results of this analysis (Table No 61).

Table 61: Comparison of change in circumstances between study groups at three months.

	Study Groups			
	Intervention Group (30)		**Control Group (86)**	
Change in circumstance	**Yes**	**No**	**Yes**	**No**
Change in doctor appointment	1 (1%)*	29 (25%)	3 (2.6%)	83 (71.6%)
Change in ability to buy GFP	7 (6%) **	23 (19.8%)	14 (12.1%) **	72 (62.1%)
New allergy to GFP	--	30 (%)	--	86 (74.1%)
New diagnosis of depression	--	30 (%)	--	86 (74.1%)
Change in Coeliac Society membership?	--	30 (%)	--	86 (74.1%)
New diagnosis of anxiety or depression	--	30 (%)	--	86 (74.1%)

*New appointments with doctor. ** Chi Square test

Change in circumstances was noted in only two criteria: appointment with doctor and ability to buy GFP. A Wilcoxon Signed-Ranks test indicated that the ability to buy GFP at three months (Mean Rank = 11) was not different from the ability to buy GFP at six months (Mean Rank = 11) $Z = -3.2$, $p < 0.01$. Additionally, no significant difference was noted at three months (Mean Rank = 4) and six months (Mean Rank = 4) $Z = -.37$, $p = .70$, in relation to doctor or dietitian appointment. This suggests that neither of these changes was significantly different in the two groups. It is thus accepted that, among the factors known to influence adherence independent of the administered intervention, there was no significant difference between the groups to account for any subsequent change.

Leffler Questionnaire:

All responders at three months (n=116) completed the Leffler questionnaire and none of the data was left blank. CDAT scores ranged from 7 to 17 (M = 10.25, SD = 2.3) and it were not distributed normally

(p<0.01), with skewness of .46 (SE = .22) and kurtosis of -.39 (SE = .44). Combined results of means from all the statements on the Leffler questionnaires are in the table below (Table no 62)

Table 62: Comparing CDAT scores of the responders at three months based on gender and ethnicity.

		Gender			Ethnicity		
	Total (n=116)	Male (n=30)	Female (n=86)		White (n=98)	Asians (n=18)	
Statements in CDAT Score	Mean ± SD	Mean ±SD	Mean ±SD	**P**	Mean ±SD	Mean ±SD	**P**
Symptoms of CD							
Low energy?	1.54 ±0.7	1.57 ± 0.7	1.53 ± 0.7	.71	1.57 ± 0.7	1.39 ± 0.6	.42
Headache	1.80 ± 0.9	1.53 ± 0.7	1.90 ± 0.9	.09	1.88 ± 0.9	1.39 ± 0.6	**.05**
Social Issue							
Follow GFD while dining out?	1.56 ± 0.7	1.63 ± 0.8	1.53 ± 0.6	.70	1.61 ± 0.7	1.28 ± 0.4	.09
Psychological							
Consider the consequences	1.52 ± 0.7	1.50 ± 0.5	1.52 ± 0.8	.44	1.55 ± 0.7	1.33 ± 0.8	.10
Don't consider myself a failure	1.44 ± 0.6	1.47 ± 0.6	1.43 ± 0.6	.64	1.50 ± 0.6	1.11 ± 0.3	**.01**
Gluten Exposure							
Accidental gluten exposures?	1.34 ± 0.5	1.30 ± 0.5	1.36 ± 0.5	.52	1.37 ± 0.6	1.22 ± 0.4	.44
Eaten gluten on purpose?	1.04 ± 0.2	1.0 ± 0.0	1.06 ± 0.2	.17	1.05 ± 0.2	1.00 ± 0.0	.32
Overall CDAT score	10.25 ± 2.3	10.0 ± 2.2	10.34 ± 2.4	**.58**	10.53 ± 2.4	8.72 ± 1.3	**.00**

The table above shows that South Asians had significantly lower mean adherence scores (suggesting better adherence to a GFD) as compared to the White Caucasians on: overall score, the psychological dimension (don't consider myself a failure) and the symptomatic dimension (headache).

Comparison of CDAT scores at baseline and at three months:

CDAT scores were compared between baseline and month three for control and intervention groups. Higher CDAT scores were noted in the intervention group pre intervention, which exhibited a significant decrement post intervention. The results are shown in the table below (Table No 63) (Appendix 4.3Hk)

Table 63: Comparing CDAT Scores of the study groups at baseline and three months

	Study Groups							
	Intervention Group				Control Group			
Statements in CDAT Score	**Baseline (n=30)** Mdn (IQR)	**Three Months (n=30)** Mdn (IQR)	**Difference (z)**	***P****	**Baseline (95)** Mdn (IQR)	**Three Months (86)** Mdn (IQR)	**Difference (z)**	***P****
Symptoms of CD								
Low energy?	3 (2-3)	3 (2-3)	0 (-3.8)	**<0.01**	1 (1-2)	1 (1-2.5)	0 (-2.3)	**.01**
Headache	3 (2-3.25)	3 (2-3.25)	0 (-1.2)	.46	1 (1-2)	1 (1-2.)	0 (-2.1)	**.03**
Social Issue								
GFD while dining out?	3 (2-3)	2 (2-3)	1 (-2.2)	.18	1 (1-2)	2 (1-2.5)	1 (-2.8)	**<0.01**
Psychological								
Consequences	1 (1-2)	1 (1-2)	0 (-1.0)	.41	1 (1-2)	1 (1-1.5)	0 (-1.4)	.15
Failure	2 (1.75-3)	2 (1.75-3)	0 (-.78)	.16	1 (1-2)	1 (1-1.5)	0 (-.09)	.92
Gluten Exposure								
Accidental exposures?	3 (2-4)	3 (2-4)	0 (-3.0)	**<0.01**	1 (1-1)	1 (1-1)	0 (-.04)	.96
Gluten on purpose?	1 (1-2)	1 (1-2)	0 (-3.0)	**<0.01**	1 (1-1)	1 (1-1)	0 (0.0)	1.0
Overall CDAT score	16 (14-17)	16 (14-17.25)	0 (-3.7)	**<0.01**	9 (8-10)	10 (8.5-10.5)	1 (-.92)	.35

It is clear from the table above that, in the intervention group, there is significant improvement in the symptom of low energy and in gluten exposure. However, in the control group, low energy symptoms improved but headache symptoms deteriorated significantly. To compare the overall CDAT scores of the intervention group (n=30), the Wilcoxon Signed-Rank test (WSRT) was performed: there was a statistically significant reduction in CDAT scores from pre-intervention (Mdn = 16, n=30) to post intervention (Mdn = 13, n=30), Z = -4.30, p < .00, r = .79. In comparison, there was no significant difference in overall CDAT scores in the control group when analysed at baseline (Mdn = 16, n=95) and at three months (Mdn = 13, n=86), Z = -.416, p= <0.01. r=.38. The bar chart below compares these groups (Fig No 36) (Appendix 4.3Hk)

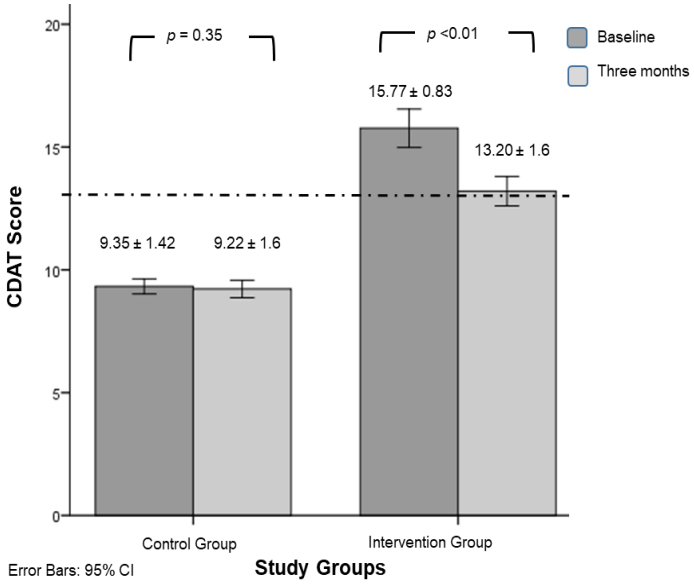

Figure 36: Comparison of CDAT scores (M±SD) of the groups at baseline (intervention; n=30, control; n=86) and then at three months. Line shows the cut-off point of the adherence (below the line CDAT score <13).

The bar chart shows that the CDAT scores of the intervention group decreased significantly. Of note the reduction for the intervention group is above the adherence line (M=13.2). Post intervention there were 73.3% (n=22) who had CDAT scores above 13, hence the intervention was effective in 26.7% (n=8) of the patients.

The improvement in adherence was also analysed from the point of view of increasing knowledge and the CDAT scores of those who showed decrement were analysed using a chi-square for independence

test: it did not indicate a significant effect of increasing knowledge on decreasing CDAT score, $\chi 2$ (1, n=30) = .66, *p*=.44, phi = .14. This suggests that increasing knowledge had no significant effect on adherence rate (Appendices 4.3Ha-k).

CD Quality of Life questionnaire at three months:

The CDQoL was completed and returned by 104 (83.2%) participants, which is a subset of the total returners (n=125) at three months. All the entries were legible and were included for analysis. The overall scores ranged from 43 to 91, (M = 61.1, SD = 13.0) and were not distributed normally (p<0.01), with skewness of .78 (SE = .23) and kurtosis of -.57 (SE = .46). Social stigma of CD was the lowest scoring area (58.08), followed by worries about CD (61.1); symptoms of CD was the highest scoring area (better quality of life). The overall index of quality of life was also compared between the two genders and for males scores ranged from 44 to 86 (M = 61.07, SD = 12.4) and were not distributed normally (P=0.00), with skewness of .76 (SE = .43) and kurtosis of -.75 (SE = .43). Similarly, the CDQoL scores for females ranged from 43 to 91 (M = 61.19, SD = 13.0) and were not distributed normally (P=0.00), with skewness of .80 (SE = .27) and kurtosis of -.51 (SE = .54). This is compared in the bar chart below (Fig No 37).

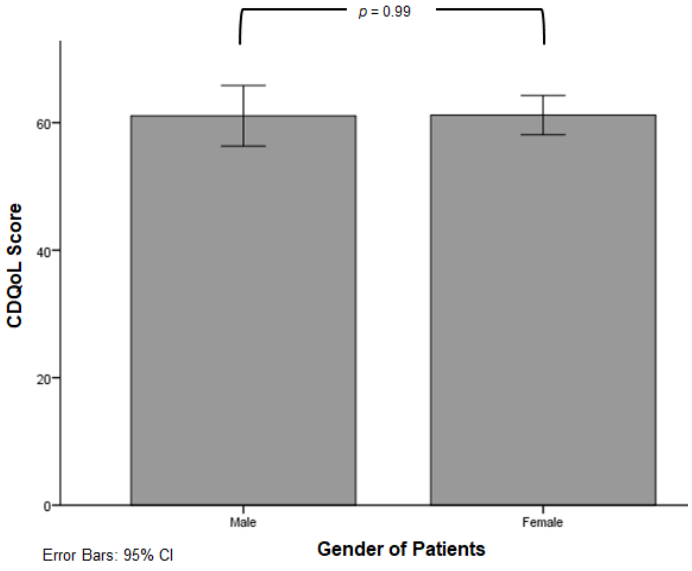

Figure 37: Comparison of CDQoL scores of males and females at three months.

MWU test showed no significant difference between the CDQoL scores of males (Mdn = 56.79, n=29) and females (Mdn = 58.0, n=75), Z = -.01, p= .99, r=.00. This means that quality of life between the two genders was not significantly different. CDQoL was next compared between patients at baseline and at three months and significance was calculated for individual dimensions as well as the overall index of CDQoL; the results are displayed in the table below (Table No 64) (Appendix 4.3Ig).

Table 64: Dimensions in relation to CDQoL compared as study progressed

	Study Groups											
	Intervention Group						Control Group					
	Baseline		Three Months				Baseline		Three Months			
Dimentions CDQoL	**Median**	**IQR**	**Median**	**IQR**	**Difference**	***P***	**Median**	**IQR**	**Median**	**IQR**	**Difference**	***P***
Stigma	46.8	37.5-60.9	46.8	39-59.3	2	0.73*	40.6	31.2-75	53.1	40.6-65.6	97	0.09*
Dietary burden	50	40.6-68.7	56.2	50-68.7	6.2	0.24*	50	43.7-71.8	65.6	53.1-71.8	100	**0.02***
Symptoms	50	45-57.5	50	40-60	0	0.94*	70	55-80	70	60-80	100	0.30*
Social isolation	50	40-77.5	50	40-65	0	0.65*	55	45-80	65	50-80	100	0.06*
Worries	58.3	50-68.7	58.3	45.8-75	0	0.30**	58.3	45.8-79.1	62	50-70	92	0.86*
Overall	49	49.8-61.9	50.33	48-55.4	1.3	0.63*	51.2	46.5-79.1	59.6	54.1-70.8	91	0.06*

***Wilcoxon Sign Rank test ** Student T test**

The overall CDQoL was compared for both groups at baseline and three months and no significant difference was noted in each dimension of HRQoL at baseline and month three. In the control group, significant difference was noted in dietary burden, where the score improved significantly (p=0.02). The intervention thus had no significant effect on changing CDQoL (Appendices 4.3I a-g)

CD knowledge of the study groups at three months:

A total of 110 (88%) patients completed the knowledge questionnaires (Silvester et al., 2016) and they were a subset of the returners (n=125) at three months. None of the questionnaires were left blank and the information was legible. Silvester scores were calculated and ranged from 12 to 17 (M = 15.42, SD = 1.09); they were non-normally distributed (p<0.01), with skewness of -.85 (SE = .23) and kurtosis of .676 (SE = .54).

A Mann-Whitney U test revealed significant difference in the Silvester score for intervention (Mdn = 13.5, n =30) and control groups (Mdn = 15, n = 80), U = 895, z = -2.6, p = .03, r = -.20. The results suggest that at three months the control group had significantly better knowledge about CD as compared to the intervention group. This difference, when further analysed, was found to be in certain food items such as: balsamic vinegar, glutinous rice, cocoa, modified starch, sausages, soy sauce and rice crisps.

CD knowledge was compared for both intervention and control groups at baseline and then at three months. Among the allowed food items, the correct responses showed improvements from base line to three months with regards to milk, chickpea flour and balsamic vinegar in both groups; this also reached significance in both groups.

A universal increase in all components of knowledge was observed in the intervention group, except a marginal drop re soy sauce. Egg noodles and milk were correctly spotted by 30 (100%) patients post intervention. Correct identification of croutons and cocoa was still an issue, although it had increased from the base line of 14 to 26 and 21 to 25 respectively. In the control group there was a variable response and both increases and decreases in the knowledge components were observed. The groups are compared in the table below (Table No 65).

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Table 65: Silvester CD questionnaires compared at baseline and at three months. The number of correct answers for each item is presented along with respective percentages

Study groups		Intervention Group (n=30)				Control group (n=80)			
		Baseline		Three months		Baseline		Three months	
		N=30	(%)	N=30	(%)	N =86	(%)	N =80	(%)
Food allowed	Milk	26	86.7	30	100	76	88.4	73	91.3
	Chickpea flour	26	86.7	29	96.7	77	89.5	72	90
	Balsamic vinegar	22	73.3	26	86.7	77	89.5	75	93.8
	Buckwheat	26	86.7	27	90.0	79	91.9	76	95
	Glutinous rice	23	76.7	27	90.0	81	94.2	78	97.5
	Cocoa	21	70.0	25	83.3	81	94.2	78	97.5
	Modified corn	22	73.3	27	90.0	82	95.3	69	86.3
Food to question	Flavoured yogurt	25	83.3	26	86.7	74	86.0	74	92.5
	Sausages	23	76.7	27	90.0	82	95.3	75	93.8
	Soy sauce	23	76.7	22	73.3	84	97.7	65	81.3
	Oatmeal	24	80.0	25	83.3	70	81.4	66	82.5
	Rice crisp	21	70.0	22	73.3	76	88.4	70	87.5
	Seafood imitation	23	80.0	25	83.3	73	84.9	75	93.8
	Croutons	14	46.7	26	86.7	38	44.2	76	97.5
Food not allowed	Malt Vinegar	25	83.3	28	93.3	76	88.4	72	90
	Spelt	25	83.3	29	96.7	76	88.4	80	100
	Egg Noodles	28	93.3	30	100	80	93.0	68	85

Total Silvester scores were compared next at baseline and at three months to see if there was a significant difference in the scores at two points in time. The Wilcoxon Signed-Rank test (WSRT) was performed and it showed that, after telephonic intervention, there was a statistically significant increase in Silvester scores of the pre intervention (Mdn = 13, n=30) and post intervention population (Mdn = 15, n=30), Z = -4.230, p <0.01, r = -.77. Similarly, comparison was also drawn between the control groups and WSRT was performed: it showed that there was a statistically significant increase in Silvester scores of the control group when analysed at baseline (Mdn = 15, n=86) and at three months (Mdn = 16, n=80), Z = -3.84, p= .00, r=.43. The bar chart below compares the groups at baseline and then at three months (Fig No 38). (Appendix 4.3Jj)

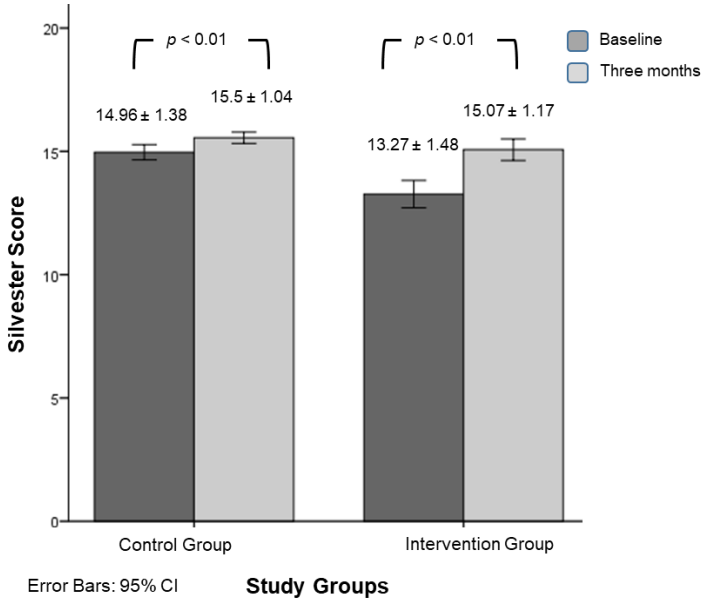

Figure 38: Comparison of Silvester scores of the population at baseline and then at three months.

This means that a significant increase in Silvester score was noted in both groups, hence an increase in knowledge about a GFD was noted at 3 months (Appendices 4.3J a-k) .

SECTION VI

Post Intervention Data at 6 Months:

At six months post intervention, 87 completed questionnaires were received and this gives a return (completion) rate of 69%. The responders from baseline and at three months are compared in the table below (Table No 66).

Table 66: Characteristics of the population at baseline, three months and at six months.

		Responders		
Variables	**Total**	**Baseline**	**Three Months**	**Six Months**
Invitations sent		**195**	**125**	**125**
	195	125 (64.1%)	116 (92.8%)	87 (69.6%)
Mean Age ± SD	50.6 ± 18.9	50.5 ± 17.7	51.2 ± 20.6	50.2 ± 17.9
Study Group	_			
Intervention	--	30 (24%)	30 (26%)	30 (34.5%)
Control	--	95 (76%)	86 (74%)	57 (65.5%)
Gender				
Male	57 (29.2%)	33 (26.4%)	30 (26%)	23 (26.4%)
Female	138 (70.7%)	92 (73.6%)	86 (74%)	64 (73.6%)
Ethnicity				
White Caucasians	170 (87.2%)	106 (84.4%)	98 (84.4%)	76 (87.4%)
South Asians	25 (12.8%)	19 (15.2%)	18 (15.5%)	11 (12.6 %)

It is clear from the table above that the drop in responders (n=9) was only noted in the control group from baseline (n=95) which dropped to 86 responders. There was no significant difference between the groups when analysed according to gender or ethnicity, which means that neither ethnicity nor gender had any effect on attrition rate.

The dropouts from the study (n=38) were analysed at six months and are presented in the table below ((Table No 67) (Appendix 4.3Ka).

Table 67: Comparison of demographics, CDAT and knowledge scores of control group at baseline and six months.

	Control group			
	Study Dropouts	**Control group**		
	Baseline (n=38)	**Baseline (n=95)**	**Six months (n=57)**	
Variables	Mdn (IQR)	Mdn (IQR)	Mdn (IQR)	*P**
Age	53 (37-67)	51 (33-64)	50 (32-64)	
CDAT score	10 (8-10)	9 (8-10)	9 (8-10)	**<0.01**
Gender	N (%)	N (%)	N (%)	
Male	10 (26.3%)	26 (27.4%)	16 (28.1%)	
Female	28 (73.7%)	69 (72.6%)	41 (71.9%)	
Ethnicity				
White Caucasian	30 (78.9%)	76 (80%)	46 (80.7%)	
South Asian	8 (21.1%)	19 (20%)	11 (19.3%)	

***WRT**

The table above shows that there was a significant difference between the knowledge and CDAT scores of the control group when compared at the two points. This means that, after attrition at six months, the control group showed better adherence (lower CDAT scores) and improved knowledge.

Assessment of change in circumstances at six months:

A total of 87 patients filled in the change in circumstances questionnaire, 30 (34%) out of which were in the intervention group and the remaining were in the control group. The table below shows the results of this analysis (Table No 68).

A change in circumstances was only noted in relation to two criteria: appointment with doctor and ability to buy GFP; but there were no significant difference between the groups. It is thus accepted that, among the known factors which could potentially change adherence to a GFD, none had significantly changed.

Table 68: Comparison of change in circumstances between study groups at three months.

	Study Groups			
	Intervention Group (n=30)		**Control Group (n=57)**	
Change in circumstance	Yes	No	Yes	No
Change in doctor appointment	1 (4%)	29 (96%)	2 (3.5%)	5 (96.5%)
Change in ability to buy GFP	6 (20%)	24 (80%)	14 (12.1%)	57 (87.9 %%)
New allergy to GFP	--	30 (100%)	--	57 (100%)
New diagnosis of depression	--	30 (100%)	--	57 (100%)
Change in Coeliac Society membership?	--	30 (100%)	--	57 (100%)
New diagnosis of anxiety	--	30 (100%)	--	57 (100%)

Comparison of CDAT score at baseline and at six months:

Having shown that no known factors are influencing the CDAT score at six months were similar in intervention and control groups, we then compared the CDAT scores from baseline (intervention Mdn= 16, control Mdn =9), month three (intervention Mdn= 13, control Mdn =9) and at six months (intervention Mdn= 13, control Mdn =8). Higher mean CDAT scores were noted in the intervention group at baseline (M=15.7 ± 2), which then decreased post intervention at six months (M=13.23 ± 1.7). It may be noted that the overall CDAT scores for the intervention group increased at month six (M=13.23 ± 1.7) as compared to month three (M=13.20 ± 1.6).

Analysing the domains of the CDAT score however, the mean for “symptom” (low energy and headache) had decreased at three months and that was maintained at month six. Similarly, on social aspects e.g. dining out, the score had maintained the previously achieved reduced levels. Additionally, psychological aspects which showed reduction at month three had increased above the baseline. Accidental gluten exposure had clearly improved at month three and was maintained at month six, with a slight increase as compared to month three. Similarly, deliberate intake of gluten had reduced at both three and six months. The control group generally maintained low scores and remained below the adherence threshold with its overall scores. The symptomatic domain showed fluctuation and the social domain showed clear improvement and this is in contrast to the intervention group. The psychological domain showed improvement and this persisted at six months. Deliberate ingestion of gluten was not an issue

in this group, but accidental exposure decreased. These groups have been compared in the table below (Table No 69) (Appendices 4.3Kg &h)

Table 69: Comparing CDAT scores of the intervention group (n=30) at baseline and six months in relation to gender.

	Study Groups					
	Intervention Groups			Control Group		
	Baseline	6 Months		Baseline	6 Months	
Statements in CDAT Score	Mdn (IQR)	Mdn (IQR)	**P***	Mdn (IQR)	Mdn (IQR)	**P***
Symptoms of CD						
Low energy?	3 (2-3)	2 (1-3)	**<0.01**	2 (1-3)	1 (1-2)	**.59**
Headache	3 (2-3.25)	2 (2-3)	.20	2 (2-3)	1 (1-1)	.58
Social Issue						
Follow GFD while dining out?	3 (2-3)	2 (1-2)	.18	2 (1-2)	1 (1-2)	**<0.01**
Psychological						
Consider the consequences	1 (1-2)	2 (1-2)	.19	2 (1-2)	1 (1-1)	.016
Don't consider myself a failure	2 (1.75-3)	2 (2-3)	1	2 (2-3)	1 (1-1)	**<0.01**
Gluten Exposure						
Accidental gluten exposures?	3 (2-4)	2 (1-2)	**<0.01**	2 (1-2)	1 (1-1)	0.96
Eaten gluten on purpose?	1 (1-2)	1 (1-1)	**.02**	1 (1-1)	1 (1-1)	0.56
Overall CDAT score	16 (14-17)	13 (12-15)	**<0.01**	13 (12-15)	8 (7-9)	**<0.01**

***WSRT**

The table shows low energy, accidental exposure and easting gluten on purpose showed significant improving. In comparison to Month three (Table No 63) It is clear that certain aspects of the CDAT score in the intervention group showed a reduction at month three, but did not show sustained reduction at month six. The control group showed baseline fluctuations in the mean score for all domains expect accidental exposure, which showed clear improvement over time. The detail fluctuations of CDAT score are shown in the table below (Table No 70).

Table 70: Comparing CDAT scores of the study groups at baseline, three months and six months.

	Study Groups											
	Intervention Group						**Control Group**					
	Baseline		Three Months		Six Months		Baseline		Three Months		Six Months	
	Mean ±SD	Mdn (IQR)	Mean ±SD	Mdn (IQR)	Mean ±SD	Mdn (IQR)	Mean ±SD	Mdn (IQR)	Mean ±SD	Mdn (IQR)	Mean ±SD	Mdn (IQR)
Symptoms of CD												
Low energy?	2.87 ± 0.93	3 (2-3)	2.13 ± 0.8	3 (2-3)	2.10 ± 0.8	2 (1-3)	1.60 ± 0.09	1 (1-2)	1.34 ±0.6	1 (1-2.5)	1.46 ±0.70	1 (1-2)
Headache	2.60 ± 1.03	3 (2-3.25)	2.43 ± 0.9	3 (2-3.25)	2.30 ± 0.8	2 (2-3)	1.37 ± 0.06	1 (1-2)	1.58 ± 0.8	1 (1-2.)	1.25 ± 0.54	1 (1-1)
Social Issue												
GFD while dining out?	2.23 ± 0.81	3 (2-3)	2.37 ± 0.8	2 (2-3)	2.0 ± 0.7	2 (1-2)	1.53 ± 0.06	1 (1-2)	1.28 ± 0.4	2 (1-2.5)	1.28 ± 0.45	1 (1-2)
Psychological												
Consequences	1.7 ± 0.87	1 (1-2)	1.63 ±0.8	1 (1-2)	1.87 ±0.7	2 (1-2)	1.32 ± 0.05	1 (1-2)	1.48 ± 0.7	1 (1-1.5)	1.12 ± 0.33	1 (1-1)
Failure	2.10 ± 0.75	2 (1.75-3)	1.83 ± 0.6	2 (1.75-3)	2.1 ± 0.75	2 (2-3)	1.31 ± 0.06	1 (1-2)	1.30 ± 0.5	1 (1-1.5)	1.07 ± 0.25	1 (1-1)
Gluten Exposure												
Accidental exposures?	2.83 ± 1.29	3 (2-4)	1.67 ± 0.7	3 (2-4)	1.70 ± 0.7	2 (1-2)	1.22 ± 0.04	1 (1-1)	1.23 ± 0.5	1 (1-1)	1.07 ± 0.25	1 (1-1)
Gluten on purpose?	1.43 ± 0.62	1 (1-2)	1.13 ± 0.3	1 (1-2)	1.17 ± 0.3	1 (1-1)	1.01 ± .10	1 (1-1)	1.01 ± 0.1	1 (1-1)	1.04 ± 0.18	1 (1-1)
Overall CDAT score	15.77 ± 0.83	16 (14-17)	13.20 ± 1.6	16 (14-17.25)	13.23 ± 1.7	13 (12-15)	9.35 ± 1.42	9 (8 -10)	9.22 ± 1.6	10 (8.5-10.5)	8.28 ± 1.23	8 (7-9)

To compare the overall CDAT scores of the intervention and control groups through time, a Wilcoxon Signed-Rank test (WSRT) was performed. It showed that, in the intervention group after telephonic intervention, there was a statistically significant reduction in CDAT score (pre-intervention (Mdn = 16, n=30) vs post intervention (Mdn = 13, n=30), Z = -4.30, p < .00, r = .79) at three months and this was sustained at six months (Mdn = 16, n=30), Z = -3.73, p < .00, r = .69. Similarly, comparison was also drawn between the control groups and WSRT was performed. It showed that there was no statistically significant reduction in CDAT scores in the control group when analysed at baseline (Mdn = 16, n=95), and three months (Mdn = 13, n=86), Z = -.927, p= .354, r=.1, although, at six months, a significant reduction was noted (Mdn = 8, n=57), Z = -7.73, p= <0.01, r=.1. The bar chart below compares these groups (Fig No 39) (Appendix 4.3Ki).

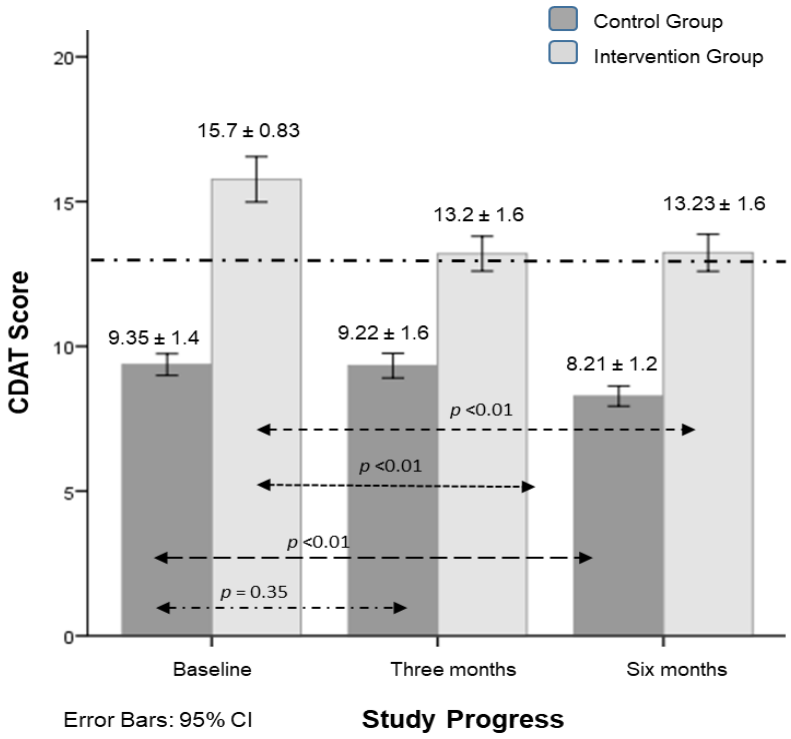

Figure 39: CDAT scores of responders at baseline, three and six months. The line shows the cut-off point for adherence (CDAT score <13).

It is clear from the chart that the overall CDAT scores decreased in the intervention group from a mean baseline score of 15.7 ±0.83 to 13.2 ±1.6 and remained at 13.23±1.6 at six months. This change is significant, which means that telephonic intervention has decreased the CDAT scores significantly, hence increased adherence to a GFD. The control group has shown a consistent decrease from a mean score of 9.35±1.42 to 9.22±1.6 at three months, but this was not significant (p=0.35). The scores

continued to drop and at six months mean scores of 8.21±1.2 were recorded; this time the decrease was significant ($p<0.01$) as compared to the baseline. It is noteworthy that in intervention group only eight (26.7%) patients achieved CDAT scores below 13 at three months and six patients (20%) remained below 13 at six months. Furthermore at no point did the mean CDAT scores drop below 13 for the intervention group (Base line M= 15.7 ± 0.83, Three months M= 13.20 ± 1.6, Six months M=13.23 ±1.6) and similarly, at no point did the CDAT scores increase above 13 for the control group (Base line M= 9.35 ± 1.4, Three months M= 9.22 ± 1.6, Six months M=8.21 ±1.2). Post intervention decrement in CDAT score was also analysed in relation to gender and the table below shows the results (Table No 71).

Table 71: Comparing CDAT scores of the intervention group (n=30) at baseline and six months in relation to gender.

	Gender					
	Male (7)			**Female (23)**		
	Baseline	6 Months		Baseline	6 Months	
Statements in CDAT Score	Mdn (IQR)	Mdn (IQR)	**P***	Mdn (IQR)	Mdn (IQR)	**P***
Symptoms of CD						
Low energy?	2 (2-3)	2 (1-3)	.25	3 (2-3)	2 (1-3)	**<0.01**
Headache	2 (2-3)	2 (2-3)	.48	3 (2-4)	2 (2-3)	.09
Social Issue						
Follow GFD while dining out?	2 (1-3)	2 (2-3)	.31	2 (2-3)	2 (1-2)	.31
Psychological						
Consider the consequences	2 (1-3)	2 (1-3)	1	1 (1-2)	2 (1-2)	.16
Don't consider myself a failure	2 (2-3)	2 (2-2)	.15	2 (1-3)	2 (2-3)	.59
Gluten Exposure						
Accidental gluten exposures?	3 (2-4)	2 (1-2)	**.05**	3 (2-4)	2 (1-2)	**<0.01**
Eaten gluten on purpose?	1 (1-2)	1 (1-1)	.31	1 (1-2)	1 (1-1)	**.03**
Overall CDAT score	16 (14-16)	14 (12-15)	**.04**	16 (14-18)	13 (12-15)	**<0.01**

***WSRT**

The above table shows that females responded to the intervention more effectively as compared to males but the overall CDAT scores showed significant decrement in both genders. This decrement was

noted in two areas: psychological and accidental exposure to the gluten. In contrast, males showed a significant improvement in accidental exposure only (Appendices 4.3K i-k). In summary, there was a significant reduction in CDAT score at both three and six months in relation to score at baseline. This suggests that the intervention was successful.

SECTION VII

Discussion

Overview

The “REST GLUTEN” telephonic intervention resulted in significant improvement in the CDAT scores in a group of patients with CD classified as not adhering to the GF diet, and this improvement was maintained at three and six months follow up, thus leading to an important clinical outcome of improving GF dietary adherence. The intervention also increased CD knowledge of the participating non-adherent CD patients. This is a seminal study, exploring the role of telephonic intervention in relation to GFD adherence. “REST GLUTEN” can be a clinical tool used by clinicians and dietitians to improve adherence to a GFD in CD patients in the future and this may be cost effective and convenient for patients who are non-adherent and as a result are at increased risk of complications of CD. This, in the long run, may well reduce economic cost for the health service in the UK and globally.

It was prospective controlled study and other designs, such as double blind randomised controlled trials, are not valid in this case and, although considered the gold standard of empirical research, placebo intervention is hypothetical and somewhat facetious in this context. Equally, face to face clinical interaction is a superior method of intervention, but it is already in vogue in clinical practice and was not the subject of this PhD. To ascertain the efficacy of telephonic/Skype® intervention in comparison to face to face interaction, a randomised study could be designed and conducted in the future. It is felt that adding another layer of human interaction i.e. Skype® may be a further improvement in this area, as it has been used in studies with variable results (Bruce et al., 2018, Max, 2017, McDade et al., 2007, Askling et al., 2002, Petrovski et al., 2015) and recommended in a review article (Armfield et al., 2015).

Study Aims and Objectives

The study met the primary aim of using a telephonic clinic to improve adherence to a GFD. The clinical relevance of the study is evident by the sustenance of low CDAT scores at three and six months follow up. But how exactly it translates into long term clinical improvement will only be evident with long term follow up of such patients. One would be looking for improvement in CD related parameters such as: improved adherence (as evidenced by dietitian and serological assessments including novel methods of GFD adherence assessment) and reduction in symptoms and complication of CD such as

osteoporosis, anaemia and mitotic disorder. This study, as an intervention, showed similar improvements at three months in CDAT scores as reported earlier by Sainsbury and colleagues (2013). The main difference and a strength of the study, however, is the selection of patients, as in this study the patients were selected from a pathological database as opposed to Sainsbury and colleagues (2013), who selected patients from online resources and an advocacy group.

The study also met the second aim of increasing knowledge of a GFD, which may enable patients to avoid inadvertent consumption of gluten containing food items, whilst at the same time not over restricting themselves from items which are gluten free. Although increasing knowledge has been linked to adherence to a GFD (Olsson et al., 2008, Hall et al., 2009, Halmos, Deng et al., 2018), our study did not find a significant link between increasing knowledge and reduction in CDAT scores (i.e. better adherence to a GFD); this is in agreement with a similar prospective randomised study by Sainsbury and colleagues (2013).

In contrast to this, Halmos and colleagues (2018), in a cross sectional survey, concluded that poor knowledge leads to incorrect identification of gluten free foods. This means that although they avoid gluten containing foods correctly (are adherent to a GFD), they wrongly identify many gluten free foods as gluten containing, thus restricts choices of food in day to day consumption (over restricting). Similarly, an earlier cross sectional study (n=82) reported possible non-adherence in patients with relatively deficient knowledge about a GFD (Silvester et al., 2016). In contrast to these studies, our study was prospective and measured GFD knowledge at two points (baseline and post intervention) and it is felt that a higher powered prospective study may well be needed to see the true effect of increasing knowledge. This theoretical improvement, if applied by the patients and if gluten containing food items are avoided, may in the long run both improve symptoms and prevent complications.

The final aim of the study, however, could not be met and no significant improvement was noticed in the HRQoL of patients in the intervention group, although, it is also evident that the HRQoL did not reduce with intervention as dietary intervention may lead to regression in HRQoL (Hauser et al., 2007). HRQoL in CD was found to significantly increased in patients in a study (n=62) by Haas et al., (2017) where 45 unique messages were sent to CD patients and HRQoL was measured by the Patients Reported Outcomes Measurement Information System (PROMIS). There are notable differences with our study, where we used a recently developed validated instrument by Croker and colleagues (20018).

Additionally, the control group in our study showed improved HRQoL and this suggests that this is a complex area (Sainsbury et al., 2013c, Ramírez-Cervantes et al., 2015, Paavola et al., 2012) and HRQoL may have been affected by unmeasured confounders. It is felt that the tool developed by Croker and colleagues (20018) to assess HRQoL in CD patients is useful and may be used in future research involving high power randomised control studies.

Study population, diagnosis of CD and return rate

The study population was all inclusive except for the paediatric age group (which was outside the scope of this research) and the number of CD patients evaluated in this research study was lower than originally planned. Our final count for participants of the study (n= 125), where 30 were randomised to the intervention group and the remaining served as a control group is comparable to Sainsbury and colleagues (2013), who randomised 101 patients in their intervention arm and 88 were included in the waitlist control arm; only 50 completed the intervention and 46 provided 3 month data. Similarly Haas and colleagues (2017) had 30 patients in their intervention group and Rajpoot et al., (2015) had 43 patients in their intervention study.

There was a female predominance in our study population, which reflected the previous trend of CD presentation in the general population (Murray et al., 2003a, Green et al., 2001) and this point has been explained in detail in relation to study I. A strength of the study was the combination of histological diagnosis of CD coupled with positive serology for increased sensitivity and specificity (Donaldson et al., 2008). This is discussed in detail in previous section (Pages 42-43). The study thus approached the diagnosis from an objective standpoint and the cohort composition was in accordance with previous research in this area.

The return rate (64%) in this study was higher than both study I and study II and this may be explained by sending repeated reminders (Silva et al., 2002, Nakash et al., 2006). Furthermore, the patients were selected from a dietitian database of patients who are under regular follow up and this too may have increased the return rate. Moreover, the return rate in this survey was not affected by age or gender (Table No 14). Our return rate compared favourably with that reported by Sainsbury and colleagues (2013) in their web based survey (14%).

Recruitment of South Asian patients was a challenging issue in this study. This was partly due to the fact that adherence was significantly higher in South Asians (comparatively less number of patients available to recruit) in our cohort, but besides this, it is the same trend which was observed in study II. Research studies involving Asians and ethnic minorities have reported low rates of Asians, especially the Muslim population in the UK (Szczepura et al., 2008). Sheldon and colleagues (2007) found that response rate was low for black and ethnic minorities, but this was in a report to NHS authorities and was poorly referenced.

Similarly, a Danish study reported the return rate in ethnic minorities be low (24%) as well (Bodewes & Kunst, 2016). Yet another UK based study (n=9,100), involving South Asians, reported a recruitment rate of 8% in a questionnaire based study (Malavige et al., 2015), which is very low. In contrast, a systematic review did not find any difference (Sykes et al., 2010) in the return rate for all non-white minorities. The low response rate among South Asians has affected the overall aims of this study, as it aimed to recruit South Asian patients as well. The question of return rate among South Asians is an under researched area and needs research by conducting interviews involving a large cohort to ascertain causes of low return and ways to increase the rate.

Study population at baseline

The difference in CDAT scores in both groups is self-explanatory, as those who had CDAT scores above 13 formed the intervention group. The median CDAT score of the whole population was 10.8; in study I, the mean CDAT score was 14.4. This discrepancy may be explained by the fact that the data from study I was from the pathology department, whereas the data from this study came from the dietetics department i.e. patients who were already under follow-up with a registered dietitian. Similarly, Sainsbury and colleagues (2013) reported a mean CDAT score of 12.2 which is marginally higher than our score; one reported by Haas et al., (2017) is 11, which is close to our score. The difference was present in all statements of CDAT score and this follows the previous research by the original author of the CDAT score (Leffler et al., 2009, Leffler et al., 2007). The reported variability in CDAT scores may be explained by differences in methodology between the studies and may well be dependent on more than one factor.

The adherence rate of our study population (76%) is much better than in study I (45%), where CDAT was used to measure the adherence rate. Adherence to a GFD was reported to be 75.8% by Villafuerte-Galvez et al., (2015) and 72.3% by Fueyo-Diaz et al., (2016), who also used CDAT as an instrument to measure the adherence rate. Variability between study I and study III may be explained by the data source as explained in the above paragraph. There is reported variability in the adherence rate (39-76%) (Leffler et al., 2009, Whitaker et al., 2009, Barratt et al., 2011, Holmes & Moor, 2012, Hall et al., 2013, Villafuerte-Galvez et al., 2015, Casellas et al., 2015, Rajpoot et al., 2015, J. Silvester et al., 2016, Sainsbury et al., 2018, Leffler et al., 2008, Muhammad et al., 2017) but this again may be explained by the methodologies used to measure the adherence. It is thus difficult to say if the reported adherence rate in our study (76%) is truly representative of the CD population, as research has also shown that, apart from differences in methodology, other factors such as ethnicity (Butterworth et al., 2004), country of origin (Fueyo-Diaz et al., 2016) and membership of advocacy groups (Hall et al., 2009, Leffler et al., 2008, Muhammad et al., 2017) may also play some role.

This study found major differences in the median CDAT score in both Caucasian and South Asian populations and this is contrary to the index study (Butterworth et al; 2005): where Asians were reported to be less adherent, we report better adherence in South Asians. Only those Asians under dietitian follow up were contacted and may well be better motivated, whilst the non-adherent South Asians are not

being followed up by a dietitian. A review of the histopathological data would have helped to clarify this issue, but equally this finding cannot be rejected based on this educated conjecture and future research is needed to clarify this point.

Reduction in CDAT score post intervention

The study observed a significant reduction in CDAT score at three months and six months post intervention, which was maintained at 6 months. The control group, in contrast to the intervention group, did not show any significant improvement in their CDAT scores (p=0.35). Our study therefore suggests that telephonic intervention may reduce CDAT score: a surrogate of adherence to a GFD. Furthermore, studies examining this area directly or indirectly related increment or decrement in CDAT scores to GFD adherence (Sainsbury et al., 2013b, Haas et al., 2017). Sainsbury et al., (2013b) evaluated their web based methodology "Bread and Butter" and Haas et al., (2017) evaluated text messaging and changes in CDAT score. Our study is similar in results to the former but different in results from the latter study especially in terms of length of follow up and patient's selection. The original proposal for our study follow up was planned to be 12 months but because of time constrains this was not possible and only data for six months is presented in the PhD although follow up data (12 months) was collected latter and is being analysed.

Although Haas et al., (2017) used mobile phone similar to us, the medium used was text messaging, which is different from our telephonic conversation. Mobile text messages have been used before with some success in relation to: weight loss (Gerber et al., 2009), as appointment reminders (Dyer, 2003) and in diabetes management (Franklin et al., 2006). Yet the authors admitted that there were limitations such as: low power of the study, selection bias and short duration of the study. In contrast to this, our study reported the same outcome of the intervention as Sainsbury et al., (2013), although different in methodology but similar in power. We feel that, among other factors (e.g. methodology, selection of patients, power of the study), it is the duration of interaction with patients which may have made "REST-Gluten" and "Bread and Butter" successful. Text messages, although instantly delivered, may lack the long term effect which comes with clinical interaction. This notion is further supported by the clinical and dietitian follow up used in the study by Rajpoot et al. (2115).

In our study, similar to the above two studies (Haas et al., 2017, Sainsbury, et al., 2013b), CDAT score was used as a surrogate of adherence to a GFD and this point is important, as novel research tools

have been developed such as: serum anti-DGP (Spatola et al., 2014), a more sensitive tool than IgA tTG (Monzani et al., 2011, Volta et al., 2008) and urine GIP (Comino et al., 2012, Moreno et al., 2017). Additionally, other experimental tools include: citrulline (Blasco Alonso et al., 2011), intestinal fatty acid-binding proteins (Oldenburger et al., 2018), autoantibodies against pancreatic secretory-granule membrane glycoprotein 2 (GP2) (Laass et al., 2015), REG Iα (Planas et al., 2011) and plasma total alkylresorcinols (Lind et al., 2016) and CDAT has not been evaluated against them. It is thus important that at some stage, the efficacy of CDAT as a research tool is evaluated in the light of a robust randomised trial to re-evaluate the use of CDAT as a research tool. It is also suggested that the novel tools such as anti-DGP should be used in research in relation to interventions aiming to increase adherence to a GFD.

CDAT is currently the best tool available and has reliability to detect adherence to a GFD as shown by several studies since its publication (Villafuerte-Galvez et al., 2015, Sainsbury et al., 2013b, Fueyo-Diaz et al., 2016, Hære et al., 2016, Nazareth et al., 2015). It is noteworthy that symptomatic, gluten exposure and psychological aspects of CDAT scores showed improvements. Among symptomatic improvement, fatigue showed significant improvement in the intervention group. Although fatigue is a well-established symptom of CD as suggested by Siniscalchi and colleagues (2005b), it is equally reported for a variety of other causes in general practice such as: depression, chronic fatigue syndrome and organic illnesses e.g. cancers, anaemia and neuro-muscular conditions. More importantly, a significant reduction was noted in the accidental and deliberate exposure to a gluten containing food item and this is relatively objective improvement in adherence to a GFD. It is interesting to note that in our study, despite an increase in the knowledge score (Silvester et al., 2016), there was no significant correlation between improvement in knowledge and adherence to a GFD.

It is noteworthy that, although significant reduction was observed in CDAT scores at month three, the median scores in the intervention group did not fall below 13, which is considered the adherence threshold by Leffler et al., (2009). They noticed that 92.2% of the study population (n=113 of 200) who exhibited excellent to very good adherence had a combined score of lower than 13. This was later used in studies by (Villafuerte-Galvez et al., 2015, Sainsbury et al., 2013b). It is not clear if this represents a true threshold for analysis of adherence, although it is accepted that rising CDAT score is related to non-adherence and *vice versa.* Determining such a cut off score by Leffler et al., (2009) was based on IgA

tTG used as an objective serological assessment for non-adherence, but it is interesting to note that the study did not analyse the IgA levels of any of their patients. Selective IgA deficiency is the most common immunoglobulin deficiency (Yel, 2010), affects 2% of CD patients (Chow et al., 2012) and leads to false negative results (McGowan et al., 2008) which may have missed a few non-adherent patients and this limitation was admitted by the authors. Additionally, anti tTG is not 100% specific and may also be found falsely elevated in other conditions such as: primary biliary cirrhosis (Bizzaro et al., 2003), rheumatoid arthritis (Picarelli et al., 2003) and chronic liver disease (Villalta et al., 2005); again comorbidity data was not available in the study. Furthermore, our study has demonstrated baseline variability in the CDAT scores in the non-adherent group. Whilst non-significant, it is important to demonstrate the fact that the score itself may mislead if any cut off values are used to determine adherence level without sensitive and specific serology as an overarching verification method.

It is felt that, although increasing CDAT score has been associated with non-adherence, the cut-off number is not easily generalizable to all populations with CD and further research is required in this area to tailor cut-off limits according to differing demographics. This could be further explored by designing a prospective study where different age and ethnic groups are followed and CDAT is measured at different points along with detailed interview and other serum and urine bio-markers at each point, to look at the baseline fluctuation of CDAT scores and possible confounders affecting this fluctuation.

At six months the intervention group still showed a significant reduction of CDAT score, although mean scores were slightly higher than the scores at three months. This means that the decrease achieved as a result of the intervention was sustained at six months. The length of follow up in this study is greater than Sainsbury and colleagues (2013) and similar to Rajpoot et al., (2015). It is the first controlled study with in the UK with longer follow up.

Interestingly, the CDAT scores of the control group, which were not significantly different than the baseline at three months, were significantly lower (improved adherence) at six months and this is despite the fact that no significant changes were noted in the circumstances to explain this. There is no simple explanation for this observation and may possibly be multifactorial or a placebo effect (Flik et al., 2017).

One such confounder may well be the “continual” educational and behavioural input from the Coeliac Society UK, although there is no data to report about the membership status of these patients. Outside

this speculation, objectively speaking, this may well be a “non-response bias” (Barclay et al., 2002, Berg, 2005), as the control group lost 38 patients and, when compared in sub-analysis, the remaining control group (n=57) showed better adherence (lower CDAT scores) and improved knowledge (better Silvester scores) when compared to baseline (n=95). Other possible causes may well be attending an educational event and bassline line fluctuation in the score, but none of these factors is likely to have caused this in isolation and a prospective cohort study of patients with higher power is needed, coupled with dietitian assessment and interview based research to ascertain the causes of reducing CDAT scores.

Knowledge and Health related Quality of Life in CD

Knowledge score at baseline and three months

Our study found a significant difference in the gluten foods knowledge between the adherent and non-adherent groups. Silvester et al., (2016) also noted such a difference, but our study went further and reported that differences in knowledge vary between food items, such as: balsamic vinegar, glutinous rice, cocoa, modified starch, sausages, soy sauce and rice crisps; and this is the first report of variability based on knowledge score. Knowledge *per se* might not achieve the desirable change(s) in behaviour if there exists a lack of motivation or lack of resources to effect such change(s). In a simple model, intervention coupled with necessary skills which lead to self-efficacy above a threshold level may bring about behavioural change(s) (Schwarzer, 2014). It is important to note that the knowledge questionnaire by Silvester at al., (2016) targets the adult audience.as opposed to Hopeman and colleagues (2012) who developed a comprehensive gluten consumption questionnaire but targeted for infants and young children. Our study demonstrated that an increase in knowledge in the intervention group at three months showed improvement in CDAT score, although this was not significant.

Knowledge about CD is attained in multiple ways, including at the time of diagnosis (in the clinician's office), follow up appointments, dietitian interactions, self-directed information gathering and membership of an advocacy group for maintenance and new information. Additionally, food packaging, gluten free signs and clear information on suitable GF foods and gluten containing foods as a public health policy may be a source of ongoing knowledge for patients. Furthermore, answers to GFP related questions made available to patients through a booklet, website or app may help achieve adherence in non-adherent patients. Knowledge may not be limited to patients, as restaurant chefs, food item handlers and providers are equally important in this context.

This whole area is under researched and apart from a few studies (Zarkadas et al., 2013, Silvester et al., 2016, Leffler et al., 2008, Sainsbury et al.,2013b, Elkin et al., 2018, Young & Thaivalappil, 2018) no major exploration has been done. Similarly, Zabolotsky and colleagues (2017) assessed the roel of an educational programme on CDAT and CDQoL and reported improvement in score post education. The details of educational strategy was not explained in the conference presentation. These studies, thus, have targeted patients as well as healthcare professionals and restaurant staff and conflicting results have been reported. Increasing knowledge has been linked to adherence to a GFD by Olson and

colleagues (2008) and Halmos et al., (2018). In contrast to this, no significant effect has been reported by Hall and colleagues (2009) in their systematic review, or by Sainsbury and colleagues (2103) in their randomised control study. It is felt that epidemiological studies need to be done to ascertain the knowledge gaps in the relevant groups and interventions designed to improve this knowledge. This may then be followed up to see its effect on adherence to a GFD. These studies may include measuring adherence in certain situations such as travelling and eating out, as CD affects everyday life.

Since the intervention group, along with improvement in knowledge, also received counselling including: motivation for the dietary modification, advice on special situations such as travelling, eating out and eating at a friend's house, it is difficult to ascertain which component of the intervention caused reduction in the CDAT score i.e. knowledge or counselling. It is, however, accepted that counselling *per se* is also a part of increasing knowledge about coping with certain situations.

In our study, we selectively excluded severe depression and in the intervention group no patient was given psychological counselling other than motivation. We however accept that the psychological state of the patient has an impact on adherence to a GFD (Halmos, Deng et al., 2018, Sainsbury et al., 2013a, Sainsbury et al., 2015). A meta-analysis of eight studies conducted by Sainsbury and colleagues (2017) suggested an association between self-reported depressive symptoms and poor adherence and another study also reported an association between intention and adherence to a GFD and perceived behavioural control (Kothe et al., 2015). It is suggested that in future research this issue is addressed and data regarding the psychological status of patients is gathered at each point in the follow up. In conclusion, there are knowledge gaps in terms of the effect of increasing knowledge on adherence and prospective cohort based research with high power is needed to see exactly how increasing Silvester scores may reduce CDAT scores and if this relationship is linear. It is suggested that the knowledge questionnaire may be modified according to cultural background and inclusion of words such as chapatti, daal and other ethnic meals may be included in future questionnaires to assess gluten knowledge.

CDQoL score at baseline and three months

Our study also did not report any significant relationship between increasing HRQoL and improvement in adherence to a GFD, even though a positive relationship between HRQoL and adherence to a GFD has been reported (Casellas et al., 2015, Nachman et al., 2009, S. D. Johnston et al., 2004). In contrast, there are studies where no consistent relationship between the two has been reported (Cranney et al., 2007, Viljamaa et al., 2005, Hallert et al., 2002, Zarkadas et al., 2013), but these studies have used different methods of HRQoL and measurement of adherence to a GFD. Additionally it is accepted that HRQoL is a multifactorial construct (Barratt et al., 2011). Haas et al., (2017) who used CDAT as a measure of adherence and Patient-Reported Outcomes Measurement Information System (PROMIS) as HRQoL measure, reported no relationship between HRQoL and CDAT score. It is thus concluded that, in view of the conflicting results in previously reported literature, our study has not established a relationship between improving HRQoL and adherence to a GFD and interventional studies are needed. It is further suggested that such intervention in future would benefit from validation by an additional objective method of adherence assessment such as dietitian assessment and newer sensitive bio-markers such a urinary GIP. Additionally, results should be interpreted in the light of patients' socioeconomic background and co-morbidities.

Several studies have reported HRQoL in CD and variable results have been reported (Zysk et al., 2018, Fera et al., 2003, Barrio et al., 2018, Cossu et al., 2017), mainly due to diversity in the choice of methodology and populations examined. In this study the Patient Reported Outcome Measure (PROM) of CDQoL detected a significant difference between the genders at baseline. Our study reported CD disease as stigma and dietary burden as the main issues reducing HRQoL in the study population. Symptomatic issues, social isolation and worries about CD were not reported to affect HRQoL in our study. One reason for this might be the fact that the patients were under regular dietitian follow up which shows improved HRQoL (Hall et al., 2009) and this is partly related to improved adherence to a GFD (Nachman et al., 2009). Dietary burden has been reported to be an issue in relation to a GFD as reported previously (Shah et al., 2014) and our findings are in accordance to that. Additionally, the gender discrepancy in HRQoL among females has also been reported in the literature (Hallert et al., 2003, Rodríguez Almagro et al., 2017) and this too is consistent with our findings. Our findings on increased

CDQoL in females three months after intervention may be related to non-responder bias as described above in relation to CD knowledge.

Our study did not detect any significant difference between the adherent and non-adherent groups based on CDQoL. This point needs more elaboration as HRQoL in CD has dual meanings i.e. potentially improved QoL because of fewer symptoms with adherence to a GFD (Mustalahti et al., 2002, Murray et al., 2004) but strict adherence to a GFD may bring social (Olsson et al., 2008) and economic issues (Zivin & Green, 2007c) which could worsen HRQoL. In our study, the domain relating to symptoms was significantly different between the groups, where the control (adherent) group had better HRQoL presumably due to better symptomatic control and in remaining four domains Stigma, and social isolation had better domains in the intervention (non-adherent) group. Our evidence in this regard may, however, be regarded as just a preliminary suggestion and as such it is accepted that this area needs high powered cohort studies with longer follow up, preferably recruiting treatment naïve patients and using CDQoL as the measuring instrument at baseline and at follow up, along with serological and urinary evidence of adherence or otherwise.

The QoL remained stable pre and post intervention as determined by the similar CDQoL values. Our main finding of similar overall CDQoL scores after the intervention denotes that either the intervention does not affect CDQoL, or there is a lag between the improvement in CDAT and CDQoL. The latter presumption needs a prospective study with longer follow up (Deepak et al., 2018). It is thus suggested that CDQoL, which has been developed by the Oxford team (Crocker et al., 2018a, Crocker et al., 2013), is easy to use and a valid instrument, but its use in studies needs long-term follow up (preferably 12 months and longer) in relation to an intervention programme to detect any change. In summary CDQoL did not change significantly as a result of our intervention and longer follow up and high powered studies are needed in the future.

Strengths and limitations of the research

Strengths

The main strength of our research lies in the sample selection to minimise the possibility of selection bias, which may be introduced at both participant identification and later at the participation level (Tripepi et al., 2010) and may threaten the external validity of the study (Yang et al., 2017). Findings can be generalised if the selection process is well-designed and the sample is representative of the study population. Subjects were thus identified from a hospital database instead of an advocacy group e.g. Coeliac Society. Selecting patients from an advocacy group was one of the weaknesses admitted by Sainsbury and colleagues (2013) in their randomised controlled study to increase adherence to a GFD. Additionally, instead of relying on patient reported diagnosis, objective histological and serological criteria were used to confirm the diagnosis; such a combination is more sensitive and specific for the diagnosis of CD (Watson, 2005, Green et al., 2005, Zevit & Shamir, 2014, Husby et al., 2012). Although group randomisation was adopted, a non-adherent control group could not be included in the study for the reasons stated above. Furthermore, one important strength of the current study is the recruitment of participants who are not adhering to the gluten free diet and a careful balance is required to capture data from this sub population of patients with coeliac disease.

Several potential biases were identified and efforts were made to minimise them. Inclusion of change in circumstances, for example, minimised confounder bias, as uncontrolled confounding in studies may affect results. We think that in doing so we have minimised this effect. In addition to that, severe depression was also excluded from the study population. Furthermore, the data collected in this study was through a previously used questionnaire and the methodology was adapted in the light of current research, thus increasing both internal and external reliability and reducing outcome misclassification and citation bias. The diagnosis of CD was made by the same pathologists and using the same standards, thus reducing inter-individual bias. Furthermore, the demographics of the population were compared in terms of age, ethnicity and gender, with a previously reported population in a similar survey targeting patients with CD.

Limitations

In this area of research, a consistent limitation is the difficulty in objectively measuring dietary adherence (Muhammad et al., 2019). The study could be strengthened by inclusion of laboratory data to increase the validity of the study findings, although this would impact upon participant burden. Forty percent attrition from the control group may have affected the data quality.

The lack of ethnic minority patients in the intervention arm is evident, although every effort was made to include ethnic minority patients in this subset of data. Indeed, such an intervention should involve ethnic communities outside the English-speaking community and ethnic patients should also be recruited, preferably in their own language, to decrease barriers to knowledge transfer, understanding and subsequent behavioural changes. As explained earlier, there were significantly more adherent ethnic minority patients, thus reducing the number of non-adherent patients for recruitment. Non participation of South Asians in research has been explained above, but this is being mentioned again to suggest that if we had had access to the larger histopathology database (estimated to be 700 patients), we could have increased the number of ethnic minority patients in the intervention group. Previous studies examining this question had either no ethnic participants or they did not report it (Sainsbury, et al., 2013b, Sainsbury et al., 2014, Haas et al., 2017, Pekki et al., 2018). One exception may be the India based study by Rajpoot et al., (2015), which only used ethnic data, but lacked White Caucasian participants. A substantial proportion of migrants to the UK are South Asians (Peach, 2006) and it is felt that inclusion of ethnic minority data is important in such studies as this will help tailor treatments according socio-cultural and religious needs.

Our study gave due importance to the linguistic needs of patients and language support was available to patients in seven languages other than English. As explained earlier, there were significantly more adherent ethnic minority patients, thus reducing the number of non-adherent patients for recruitment. Non participation of South Asians in research has been explained above, but this is being mentioned again to suggest that if we had had access to the larger histopathology database (estimated to be 700 patients), we could have increased the number of ethnic minority patients in the intervention group.

It is accepted that our data collection may have been selective and inadequate to fully explain complex issues of non-adherence to a GFD as this construct (a dietary habit) is affected by a variety of social,

cultural and cognitive issues; high powered studies may overcome this. In addition, the choice of a questionnaire as the research method can have serious effects on data quality (Bowling, 2005) and, despite efforts, sampling may be selective (Andrews et al., 2003).

Our study may also have a low return rate but this *per se* is not synonymous with unreliable results (Holbrook et al., 2007, Keeter et al., 2006, Curtin et al., 2000). A study comparing relative risk estimation from two studies with different return rates reported comparable and consistent results (Mealing et al., 2010) and this notion is also supported by a meta-analysis (Cook et al., 2000). It is accepted that there may be some selection bias, since the participants who responded may be more motivated and perhaps therefore more likely to adhere to a GFD. Furthermore, participants may change their behaviour when they know they are being observed; this is known as the Hawthorne effect (McCarney et al., 2007, Adair, 1984) and it may affect the results. The questionnaire method of survey excludes certain groups such as blind and visually impaired people, as special arrangements were not in place (such as the tactile reading system, Braille (Kaczmarski & Wolff, 2007) or audio supported questionnaires (Kirchner & Schmeidler, 2001)) but it is assumed that we might have missed just a few patients, which should not have affected the data quality. Finally, the authenticity of this type of research is always in question, as it is difficult to ascertain who completed each questionnaire. We acknowledge that this is one of the limitations of the study and this phenomenon may be avoided by the use of Skype or telephone administered questionnaires.

Implications of this research

The study findings must be interpreted with caution and must be taken in context before generalisation about the effective role of a telephonic clinic in the management of adherence rate is suggested. A detailed cost analysis and further research is needed to see if improved adherence rate to a GFD is indeed related to reduction in complications and improved HRQoL in a subset of previously non-adherent CD patients. A strength of our study is how its conception and design were informed by people with CD who were not adhering to a GFD.

A future direction could involve telephonic conversation and supplementing it with video link software and this could be adapted as an educational and motivational strategy. There is evidence from CD and IBS related webinars developed by the Somerset group (2018) that it has increased confidence by 84%,

has 100% acceptability and has reduced the need for clinical appointments by 50%. Additionally, it is felt that any future interventional strategy should have a focus group discussion involving motivated representatives from gastroenterology and dietetic departments who have special interest in CD and a broad spectrum of patients with CD. Further research could compare the effectiveness of a telephone clinic compared with standard face-to-face consultation.

Conclusions

This study has demonstrated that a telephonic clinic can impact upon GF knowledge and GF dietary adherence score, and maintain the improvement for 6 months. This is a novel finding globally and has potential far-reaching clinical relevance. The study findings must be interpreted with caution and the limitations of the study must be taken in context. Extending this study would be feasible with more participants, employing mixed methods of delivery, supplementing information provided by the patients with clinical letters and computerised data and external validation with sero-pathological evidence. A limitation is relatively low power and a lack of resources to support the engagement of ethnic patients. The research field of increasing adherence to a GFD is a complex area and there is a paucity of research and grants. This study has address the research aim.

Although it was a well-designed study, future improvements in this research may include: recruiting a high powered sample from a pathology database, assessing adherence to a GFD with the CDAT questionnaire coupled with novel urinary and serum bio-markers, inclusion of a non-adherent control group, participants from ethnic minority and longer follow up e.g. for twelve months.

Chapter Five

General conclusion and overall discussion

Studies presented in this PhD holistically evaluated different aspects of CD in mixed cohorts i.e. demographic evaluation, measurement of adherence to a GFD, design and delivery of intervention to increase adherence to a gluten free diet. This has not only added to the knowledge gap but has also opened the role of telephonic clinic in the follow up of CD, which may have both clinical and economic implications in the future. It is, however, possible that not all answers may have been conclusive and further research is needed to explore these areas. This section will summarise each study and consider the future prospects of each study

STUDY I

The study revisited the adherence to a GFD in the Leicester area my previous research (Muhammad, 2013), even with a larger cohort no major differences were identified. The study findings were published in Nutrients at a time (2017) when public consultation in relation to gluten free products was at a preliminary stages and our study was cited as one of the strongest pieces of evidence by NHS England for a link between prescribing and adherence in their recent document (NHS, 2018a). As a result, this may affect access to GFP for certain patients groups and this may also affect adherence to a GFD but higher powered studies are needed to explore this point of immense practical importance. Since long-term adherence is related to CD in remission and equally affected by cost and availability of GFP on prescription, as suggested by our study, a logical recommendation from our study is to make GFD available on prescription and within the reach of all patients. One of the other findings was related to food labelling and again the logical recommendation from our study will be to revise the way we present nutritional information as well as well as the gluten content of food items. It is suggested that the gluten free industry may follow the organic food industry in presenting their gluten free products with a clear and prominent message on all food items as it is possible that pictorial message of a food item being gluten free may not be enough, but more research is needed in this particular area.

Management of CD in South Asians, although not a direct focus of this study, also came under discussion. The availability of CD related literature and tailored advice, preferably in a person's own language, about the hidden gluten in ethnic meals may evolve as a specialist area in dietetics where

ethnicity specific advice may be given to patients. It is anticipated that future studies will aim to conduct research in this area.

Membership of the Coeliac UK, although an important factor in maintaining adherence to a GFD, was not universally accepted, as found by our study. This area too needs further research to evaluate the causes behind lack of membership of the Coeliac UK among CD patients. Although there is a minimal subscription fee for patients, it still needs evaluation if this may be made optional for certain patient groups such as those in changing economic situations as this may increase the membership of the body and as a result may well improve the adherence to a GFD among affected patients.

The main lesson from this study is perhaps that the adherence rate in the Leicestershire area is very close to the national average and there are definitive reasons behind that. Addressing these reasons will include: educating patients in outpatient departments about food labelling, encouraging joining the CS and, last but not least, providing them with support when needed. This study also provides a base for the design of future questionnaire studies in this area. It is perceived that despite its shortcomings, this study evaluated basic demographics and adherence rates in a mixed cohort of CD patients in Leicestershire and may well be a milestone for CD research for future studies.

STUDY II and III

This group of studies, combined in a logical sequence, designed and delivered a unique and successful intervention plan in relation to CD. Study II has given a distinctive view of a multi-ethnic population to design interventions aimed at increasing adherence to a GFD. Whilst acknowledging its limitations, this study has strengthened the viewpoint that patients are valuable assets in all aspects of the treatment and management of chronic diseases, including the design of interventions and service development. Additionally, the design of the intervention was developed in one geographical area and the intervention was conducted in another geographical area and this illustrates the general applicability of the interventional plan which is devoid of geographical bounds.

The study adapted a methodology for intervention which was patient centred and this methodology may well be a way forward for the design of such interventions in CD. The concept of involving patients in their care is not novel but its use in the design of intervention through an interview process is both innovative and practical. This study could be extended in a variety of ways, such as: including more participants (e.g. members of the Coeliac Society and paediatric patients), employing Skype® or other

video based interfaces, changing the questioning strategy, providing information about possible interventions to patients pre-interview, providing funding for the proposed intervention and combining different methods such as CD day conference followed by individual advice and motivational work.

Study III, although used a different cohort, is inseparable from study II. This highlights the general applicability or generalisation of an intervention where an idea was developed in one geographic region and was tested in another geographic region. The successful result, thus, contributed to knowledge and this is a stronger case for rolling out telephonic clinics in an already stretched NHS, where physicians, in their own time may conduct follow up clinics for selected groups of patents. This may be economically suitable to both patients as well as the NHS as an organisation.

A detailed economic analysis of telephonic clinic is the first step in such business plans and this should take into consideration the time taken by physician and dietitian. Most NHS trusts, usually, offer 15 to 20 minutes per outpatient's clinic in a follow up and structuring the whole discussion in this timeframe is possible. Such clinics may also use a tele-video interface such as Skype® which is already in use in the NHS for business meetings and interviews. Furthermore, in such clinics there is no need for outpatient nurses time, which may be freed up for other clinics, hence a saving in the long term. Although some degree of clerical support is required for running such clinics, it is perceived that it is less intense. Although it was a well-designed study, future improvements in this research may include: recruiting a higher powered sample from a pathology database, assessing adherence to a GFD with the CDAT questionnaire coupled with novel urinary and serum bio-markers, inclusion of a non-adherent control group and longer follow up e.g. for twelve months.

Conclusion

This research has opened a new avenue for design of interventions in relation to improving adherence to a GFD which is both cost effective and less dependent on technology. It is also felt that this may have a positive role in the long term control of CD and preventing complications of CD. Equally, this may also be cost effective although formal cost analysis will be required. It is recommended that future research should refine the methodology we have used by incorporating a video interface i.e. Skype® or Zoom® in the telephonic clinic and assessment of post intervention adherence should include clinical, serological and novel urinary tests so that greater objectivity may be achieved in ascertaining adherence to a GFD. We also think that the sequence of studies in this PhD may well provide guidance targeting

other area in healthcare where adherence to certain therapeutic and dietetic advice is deemed necessary i.e. diabetes and caloric intake or even following a prescribed dietary regimen or exercise in such patients. Keeping in view the protean nature of adherence in CD, major recommendations from this PhD will be to individually tailor dietary advice to each patient with CD, preferably in a language (s)he understands and to monitor adherence to a GFD by adapting both clinical and laboratory methods. Furthermore complete dietary assessment of non-adherent patients' needs to be done formally along with causes for non-adherence i.e. social, dietary and or cultural and they need to be addressed on their merits. These causes may then be approached through a one to one or group telephonic intervention which may or may not include video interface. Although the studies in this PhD attempted to evaluate a cohort of mixed ethnicities and was successful in recruiting South Asians in the first two studies but was not able to recruit any South Asian people for the third study and further work should investigate the effectiveness of such an intervention in different ethnic minorities.

The publication associated with this research has already been cited in recent literature (n=15) in relation to several themes including the availability of GFD on prescription (Walker et al., 2019), accessibility of a GFD to patients (Jeans & Hanci, 2019), CD related QoL (Zysk et al., 2019) and a systematic review by Xhakollari and colleagues (2018).

In conclusion, it is possible to say that the PhD has achieved the main aim of improving adherence to a GFD in patients with CD approaching this issue in a methodical way by selecting patients with CD who were objectively diagnosed, by arranging interviews to ascertain a cost effective and easily deliverable intervention which showed a sustained improvement. The methods described and the results achieved however may now be formally tried in day to day clinical practice to see its practical application and cost effectiveness to the NHS in log run.

References:

Abbas, A., Shahab, T., Sherwani, R.K. & Alam, S. (2018) Addition of a short course of prednisolone to a gluten-free diet vs. gluten-free diet alone in recovery of celiac disease: A pilot randomized controlled trial. *Cureus.* 10(1) pp.e2118.

Abbas, Z., Raza, S., Yakoob, J., Abid, S., Hamid, S., Shah, H. & Jafri, W. (2013) Varied presentation of celiac disease in pakistani adults. *Journal of the College of Physicians and Surgeons--Pakistan : JCPSP.* 23(7) pp.522-524.

Abenavoli, L., Proietti, I., Leggio, L., Ferrulli, A., Vonghia, L., Capizzi, R., Rotoli, M., Amerio, P.L., Gasbarrini, G. & Addolorato, G. (2006) Cutaneous manifestations in celiac disease. *World Journal of Gastroenterology : WJG.* 12(6) pp.843-852.

Abu-Janb, N. (2018) *Facilitators and Barriers to Adherence to a Gluten-Free Diet among Adults with Celiac Disease: A Systematic Review.*

Ackerman, I.N., Buchbinder, R. & Osborne, R.H. (2013) Factors limiting participation in arthritis self-management programmes: An exploration of barriers and patient preferences within a randomized controlled trial. *Rheumatology (Oxford, England).* 52(3) pp.472-479.

ACS, 2. (2016) *American Coeliac Society.* Available at: http://www.americanceliacsociety.org/ . (Accessed: 19 February 2019).

Adair, J.G. (1984) The hawthorne effect: A reconsideration of the methodological artifact. *Journal of Applied Psychology.* 69(2) pp.334.

Adam, U.U., Melgies, M., Kadir, S., Henriksen, L. and Lynch, D., 2019. Coeliac disease in Caucasian and South Asian patients in the North West of England. Journal of Human Nutrition and Dietetics.

Adams, F. (1856) *The Extant Works of Aretaeus: The Cappadocian.* Sydenham Society.

Aday, L.A. & Cornelius, L.J. (2006) *Designing and Conducting Health Surveys: A Comprehensive Guide.* John Wiley & Sons.

Addolorato, G., De Lorenzi, G., Abenavoli, L., Leggio, L., Capristo, E. & Gasbarrini, G. (2004) Psychological support counselling improves gluten-free diet compliance in coeliac patients with affective disorders. *Alimentary Pharmacology & Therapeutics.* 20(7) pp.777-782.

Admou, B., Essaadouni, L., Krati, K., Zaher, K., Sbihi, M., Chabaa, L., Belaabidia, B. & Alaoui-Yazidi, A. (2012) Atypical celiac disease: From recognizing to managing. *Gastroenterology Research and Practice.* 2012.

Aggarwal, S., Lebwohl, B. & Green, P.H. (2012) Screening for celiac disease in average-risk and high-risk populations. *Therapeutic Advances in Gastroenterology.* 5(1) pp.37-47.

Agrawal, S., Gupta, A., Yachha, S., Müller-Myhsok, B., Mehrotra, P. & Agarwal, S. (2000) Association of human leucocyte-DR and DQ antigens in coeliac disease: A family study. *Journal of Gastroenterology and Hepatology.* 15(7) pp.771-774.

Akbari, M.R., Mohammadkhani, A., Fakheri, H., Zahedi, M.J., Shahbazkhani, B., Nouraie, M., Sotoudeh, M., Shakeri, R. & Malekzadeh, R. (2006) Screening of the adult population in iran for coeliac disease: Comparison of the tissue-transglutaminase antibody and anti-endomysial antibody tests. *European Journal of Gastroenterology & Hepatology.* 18(11) pp.1181-1186.

Akobeng, A.K., Ramanan, A.V., Buchan, I. & Heller, R.F. (2006) Effect of breast feeding on risk of coeliac disease: A systematic review and meta-analysis of observational studies. *Archives of Disease in Childhood.* 91(1) pp.39-43.

Al Ali, A.A. & Elzubair, A.G. (2016) Establishing rapport: Physicians' practice and attendees' satisfaction at a primary health care center, dammam, saudi arabia, 2013. *Journal of Family & Community Medicine.* 23(1) pp.12-17.

Alaedini, A., Green, P.H., Sander, H.W., Hays, A.P., Gamboa, E.T., Fasano, A., Sonnenberg, M., Lewis, L.D. & Latov, N. (2002) Ganglioside reactive antibodies in the neuropathy associated with celiac disease. *Journal of Neuroimmunology.* 127(1-2) pp.145-148.

Al-Hussaini, A., Troncone, R., Khormi, M., AlTuraiki, M., Alkhamis, W., Alrajhi, M., Halal, T., Fagih, M., Alharbi, S. & Bashir, M.S. (2017) Mass screening for celiac disease among school-aged children: Toward exploring celiac iceberg in saudi arabia. *Journal of Pediatric Gastroenterology and Nutrition.* 65(6) pp.646-651.

Aloia, C.R., Gasevic, D., Yusuf, S., Teo, K., Chockalingam, A., Patro, B.K., Kumar, R. & Lear, S.A. (2013) Differences in perceptions and fast food eating behaviours between indians living in high-and low-income neighbourhoods of chandigarh, india. *Nutrition Journal.* 12(1) pp.4.

Altobelli, E., Paduano, R., Petrocelli, R. & Di Orio, F. (2014) Burden of celiac disease in europe: A review of its childhood and adulthood prevalence and incidence as of september 2014. *Annali Di Igiene : Medicina Preventiva E Di Comunita.* 26(6) pp.485-498.

Amarapurkar, D.N., Somani, V.S., Shah, A.S. & Kankonkar, S.R. (2016) HLA–DQ genotyping in celiac disease in western india. *Tropical Gastroenterology.* 36(3) pp.174-178.

Annibale, B., Severi, C., Chistolini, A., Antonelli, G., Lahner, E., Marcheggiano, A., Iannoni, C., Monarca, B. & Delle Fave, G. (2001) Efficacy of gluten-free diet alone on recovery from iron deficiency anemia in adult celiac patients. *The American Journal of Gastroenterology.* 96(1) pp.132-137.

Aquilino, W.S. (1994) Interview mode effects in surveys of drug and alcohol use: A field experiment. *Public Opinion Quarterly.* 58(2) pp.210-240.

Armfield, N.R., Bradford, M. & Bradford, N.K. (2015) The clinical use of skype—for which patients, with which problems and in which settings? A snapshot review of the literature. *International Journal of Medical Informatics.* 84(10) pp.737-742.

Arnone, J. & Fitzsimons, V. (2012) Adolescents with celiac disease: A literature review of the impact developmental tasks have on adherence with a gluten-free diet. *Gastroenterology Nursing : The Official Journal of the Society of Gastroenterology Nurses and Associates.* 35(4) pp.248-254.

Aronson, J.K. (2007) Compliance, concordance, adherence. *British Journal of Clinical Pharmacology.* 63(4) pp.383-384.

Aronsson, C.A., Lee, H., Koletzko, S., Uusitalo, U., Yang, J., Virtanen, S.M., Liu, E., Lernmark, Å, Norris, J.M. & Agardh, D. (2016) Effects of gluten intake on risk of celiac disease: A case-control study on a swedish birth cohort. *Clinical Gastroenterology and Hepatology.* 14(3) pp.403-409. e3.

Asch, D.A., Jedrziewski, M.K. & Christakis, N.A. (1997) Response rates to mail surveys published in medical journals. *Journal of Clinical Epidemiology.* 50(10) pp.1129-1136.

Ascher, H., Krantz, I., Rydberg, L., Nordin, P. & Kristiansson, B. (1997) Influence of infant feeding and gluten intake on coeliac disease. *Archives of Disease in Childhood.* 76(2) pp.113-117.

Ashton-Key, M., Diss, T.C., Pan, L., Du, M.Q. & Isaacson, P.G. (1997) Molecular analysis of T-cell clonality in ulcerative jejunitis and enteropathy-associated T-cell lymphoma. *The American Journal of Pathology.* 151(2) pp.493-498.

Askling, J., Linet, M., Gridley, G., Halstensen, T.S., Ekström, K. & Ekbom, A. (2002) Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. *Gastroenterology.* 123(5) pp.1428-1435.

Assor, E., Marcon, M.A., Hamilton, N., Fry, M., Cooper, T. & Mahmud, F.H. (2015) Design of a dietary intervention to assess the impact of a gluten-free diet in a population with type 1 diabetes and celiac disease. *BMC Gastroenterology.* 15(1) pp.1.

Austin, L.L. & Dobbins, W.O. (1988) Studies of the rectal mucosa in coeliac sprue: The intraepithelial lymphocyte. *Gut.* 29(2) pp.200-205.

Avis, M., Bond, M. & Arthur, A. (1995) Exploring patient satisfaction with out-patient services. *Journal of Nursing Management.* 3(2) pp.59-65.

Aziz, D.A., Kahlid, M., Memon, F. & Sadiq, K. (2017) Spectrum of celiac disease in paediatric population: Experience of tertiary care center from pakistan. *Pakistan Journal of Medical Sciences.* 33(6) pp.1301.

Aziz, I., Karajeh, M.A., Zilkha, J., Tubman, E., Fowles, C. & Sanders, D.S. (2014) Change in awareness of gluten-related disorders among chefs and the general public in the UK: A 10-year follow-up study. *European Journal of Gastroenterology & Hepatology.* 26(11) pp.1228-1233.

Babbie, E.R. (1989) *The Practice of Social Research.* Wadsworth Publishing Company.

Bahrani, K., Singh, M.B., Bhatia, R., Prasad, K., Vibha, D., Shukla, G., Vishnubhatla, S. & Patterson, V. (2017) Telephonic review for outpatients with epilepsy—A prospective randomized, parallel group study. *Seizure.* 53pp.55-61.

Bai, D., Brar, P., Holleran, S., Ramakrishnan, R. & Green, P.H. (2005) Effect of gender on the manifestations of celiac disease: Evidence for greater malabsorption in men. *Scandinavian Journal of Gastroenterology.* 40(2) pp.183-187.

Bakker, S., Pouwer, F., Tushuizen, M., Hoogma, R., Mulder, C. & Simsek, S. (2013) Compromised quality of life in patients with both type 1 diabetes mellitus and coeliac disease. *Diabetic Medicine.* 30(7) pp.835-839.

Bakshi, A., Stephen, S., Borum, M.L. & Doman, D.B. (2012) Emerging therapeutic options for celiac disease: Potential alternatives to a gluten-free diet. *Gastroenterology & Hepatology.* 8(9) pp.582.

Bannister, E.G., Cameron, D.J., Ng, J., Chow, C.W., Oliver, M.R., Alex, G., Catto-Smith, A.G., Heine, R.G., Webb, A. & McGrath, K. (2014) Can celiac serology alone be used as a marker of duodenal mucosal recovery in children with celiac disease on a gluten-free diet? *The American Journal of Gastroenterology.* 109(9) pp.1478.

Barada, K., Bitar, A., Mokadem, M.A., Hashash, J.G. & Green, P. (2010) Celiac disease in middle eastern and north african countries: A new burden? *World Journal of Gastroenterology : WJG.* 16(12) pp.1449-1457.

Barclay, S., Todd, C., Finlay, I., Grande, G. & Wyatt, P. (2002) Not another questionnaire! maximizing the response rate, predicting non-response and assessing non-response bias in postal questionnaire studies of GPs. *Family Practice.* 19(1) pp.105-111.

Bardella, M.T., Fredella, C., Prampolini, L., Marino, R., Conte, D. & Giunta, A.M. (2000) Gluten sensitivity in monozygous twins: A long-term follow-up of five pairs. *The American Journal of Gastroenterology.* 95(6) pp.1503-1505.

Bardella, M., Velio, P., Cesana, B., Prampolini, L., Casella, G., Di Bella, C., Lanzini, A., Gambarotti, M., Bassotti, G. & Villanacci, V. (2007) Coeliac disease: A histological follow-up study. *Histopathology.* 50(4) pp.465-471.

Barratt, S.M., Leeds, J.S. & Sanders, D.S. (2013) Factors influencing the type, timing and severity of symptomatic responses to dietary gluten in patients with biopsy-proven coeliac disease. *Journal of Gastrointestinal & Liver Diseases.* 22(4) .

Barratt, S.M., Leeds, J.S. & Sanders, D.S. (2011) Quality of life in coeliac disease is determined by perceived degree of difficulty adhering to a gluten-free diet, not the level of dietary adherence ultimately achieved. *Journal of Gastrointestinal and Liver Diseases : JGLD.* 20(3) pp.241-245.

Barriball, K.L., Christian, S.L., While, A.E. & Bergen, A. (1996) The telephone survey method: A discussion paper. *Journal of Advanced Nursing.* 24(1) pp.115-121.

Barrio, J., Cilleruelo, M.L., Román, E. & Fernández, C. (2018) Health-related quality of life in spanish coeliac children using the generic KIDSCREEN-52 questionnaire. *European Journal of Pediatrics.* 177(10) pp.1515-1522.

Barsade, S.G. (2002) The ripple effect: Emotional contagion and its influence on group behavior. *Administrative Science Quarterly.* 47(4) pp.644-675.

Baruch, Y. & Holtom, B.C. (2008) Survey response rate levels and trends in organizational research. *Human Relations.* 61(8) pp.1139-1160.

Bascunan, K.A., Vespa, M.C. & Araya, M. (2017) Celiac disease: Understanding the gluten-free diet. *European Journal of Nutrition.* 56(2) pp.449-459.

Bazeley, P. & Jackson, K. (2013) *Qualitative Data Analysis with NVivo.* Sage Publications Limited.

Bebb, J., Lawson, A., Knight, T. & Long, R. (2006) Long-term follow-up of coeliac disease–what do coeliac patients want? *Alimentary Pharmacology & Therapeutics.* 23(6) pp.827-831.

Belei, O., Dobrescu, A., Heredea, R., Iacob, E.R., David, V. & Marginean, O. (2018) Histologic recovery among children with celiac disease on a gluten-free diet. A long-term follow-up single-center experience. *Archives of Medical Science: AMS.* 14(1) pp.94.

Bender, E. (2016) Student-centered teaching. http://www.ericabender.com/uploads/6/5/7/4/65747191/student-centered_teaching.pdf (Accessed 19 February, 2019)

Berg, Nathan, Non-Response Bias (2005). Encyclopaedia of Social Measurement, Vol. 2, pp. 865-873, Kempf-Leonard, K., ed., London, Academic Press . available at: https://poseidon01.ssrn.com/delivery.php?ID=287114112074119093094083078094026028127035061037007087028124073125101070075086098105101029122061103047118073112001003073019068013074027021053115118107012018085072058089039086071115088004097113096026016118082094008081001111003098001003073001074103100&EXT=pdf (Accessed, 19 February, 2019)

Bergamaschi, G., Markopoulos, K., Albertini, R., Di Sabatino, A., Biagi, F., Ciccocioppo, R., Arbustini, E. & Corazza, G.R. (2008) Anemia of chronic disease and defective erythropoietin production in patients with celiac disease. *Haematologica.* 93(12) pp.1785-1791.

Bernard, H.R. (2011) *Research Methods in Anthropology: Qualitative and Quantitative Approaches.* Rowman Altamira.

Bernardo, D. & Pena, A.S. (2012) Developing strategies to improve the quality of life of patients with gluten intolerance in patients with and without coeliac disease. *European Journal of Internal Medicine.* 23(1) pp.6-8.

Bernini, P., Bertini, I., Calabro, A., la Marca, G., Lami, G., Luchinat, C., Renzi, D. & Tenori, L. (2010) Are patients with potential celiac disease really potential? the answer of metabonomics. *Journal of Proteome Research.* 10(2) pp.714-721.

Berry, N., Basha, J., Varma, N., Varma, S., Prasad, K.K., Vaiphei, K., Dhaka, N., Sinha, S.K. & Kochhar, R. (2018) Anemia in celiac disease is multifactorial in etiology: A prospective study from india. *JGH Open.* 2(5) pp.196-200.

Bhadada, S.K., Kochhar, R., Bhansali, A., Dutta, U., Kumar, P.R., Poornachandra, K.S., Vaiphei, K., Nain, C.K. & Singh, K. (2011) Prevalence and clinical profile of celiac disease in type 1 diabetes mellitus in north india. *Journal of Gastroenterology and Hepatology.* 26(2) pp.378-381.

Bhattacharya, M., Dubey, A. & Mathur, N. (2009) Prevalence of celiac disease in north indian children.

Bhattacharya, M., Kapoor, S. & Dubey, A.P. (2013) Celiac disease presentation in a tertiary referral centre in india: Current scenario. *Indian Journal of Gastroenterology.* 32(2) pp.98-102.

Bhatti, A., Mahida, V. & Gupte, S. (2007) Iron status of hindu brahmin, jain and muslim communities in surat, gujarat. *Indian Journal of Hematology and Blood Transfusion.* 23(3-4) pp.82-87.

Biagi, F., Lorenzini, P. & Corazza, G. (2000) Literature review on the clinical relationship between ulcerative jejunoileitis, coeliac disease, and enteropathy-associated T-cell lymphoma. *Scandinavian Journal of Gastroenterology.* 35(8) pp.785-790.

Biagi, F., Vattiato, C., Agazzi, S., Balduzzi, D., Schiepatti, A., Gobbi, P. & Corazza, G.R. (2014) A second duodenal biopsy is necessary in the follow-up of adult coeliac patients. *Annals of Medicine.* 46(6) pp.430-433.

Biagi, F., Andrealli, A., Bianchi, P.I., Marchese, A., Klersy, C. & Corazza, G.R. (2009) A gluten-free diet score to evaluate dietary compliance in patients with coeliac disease. *The British Journal of Nutrition.* 102(6) pp.882-887.

Biagi, F., Bianchi, P.I., Marchese, A., Trotta, L., Vattiato, C., Balduzzi, D., Brusco, G., Andrealli, A., Cisaro, F., Astegiano, M., Pellegrino, S., Magazzu, G., Klersy, C. & Corazza, G.R. (2012) A score that verifies adherence to a gluten-free diet: A cross-sectional, multicentre validation in real clinical life. *The British Journal of Nutrition.* 108(10) pp.1884-1888.

Bianchi, M. & Bardella, M.T. (2008) Bone in celiac disease. *Osteoporosis International.* 19(12) pp.1705-1716.

Biesiekierski, J.R. (2017) What is gluten? *Journal of Gastroenterology and Hepatology.* 32pp.78-81.

Bingley, P.J., Williams, A.J., Norcross, A.J., Unsworth, D.J., Lock, R.J., Ness, A.R., Jones, R.W. & Avon Longitudinal Study of Parents and Children Study Team (2004) Undiagnosed coeliac disease at age seven: Population based prospective birth cohort study. *BMJ (Clinical Research Ed.).* 328(7435) pp.322-323.

Bird, L.G., Pilkington, C.L., Saputra, A. & Serventi, L. (2017) Products of chickpea processing as texture improvers in gluten-free bread. *Food Science and Technology International.* 23(8) pp.690-698.

Birmingham City Council (2018) ***Ethnic Groups in Birmingham. 2018 KS201 Ethnic Group***. Available at: https://www.birmingham.gov.uk/downloads/file/9741/2018_ks201_ethnic_group (Accessed: 19 February 2019).

Bischoff-Ferrari, H.A., Giovannucci, E., Willett, W.C., Dietrich, T. & Dawson-Hughes, B. (2006) Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *The American Journal of Clinical Nutrition.* 84(1) pp.18-28.

Bizzaro, N., Villalta, D., Tonutti, E., Doria, A., Tampoia, M., Bassetti, D. & Tozzoli, R. (2003) IgA and IgG tissue transglutaminase antibody prevalence and clinical significance in connective tissue diseases, inflammatory bowel disease, and primary biliary cirrhosis. *Digestive Diseases and Sciences.* 48(12) pp.2360-2365.

Black, J.L. & Orfila, C. (2011) Impact of coeliac disease on dietary habits and quality of life. *Journal of Human Nutrition and Dietetics : The Official Journal of the British Dietetic Association.* 24(6) pp.582-587.

Bland, M. (2015) *An Introduction to Medical Statistics.* Oxford University Press (UK).

Blasco Alonso, J., Serrano Nieto, J., Navas Lopez, V.M., Barco Galvez, A., Vicioso, I., Carazo Gallego, B., Ortiz Perez, P. & Sierra Salinas, C. (2011) Plasma citrulline as a marker of loss of enterocitary mass in coeliac disease in childhood. *Nutricion Hospitalaria.* 26(4) pp.807-813.

Bodewes, A.J. & Kunst, A.E. (2016) Involving hard-to-reach ethnic minorities in low-budget health research: Lessons from a health survey among moluccans in the netherlands. *BMC Research Notes.* 9(1) pp.319.

Boeije, H. (2002) A purposeful approach to the constant comparative method in the analysis of qualitative interviews. *Quality & Quantity.* 36(4) pp.391-409.

Bohdanowicz, P. (2006) Environmental awareness and initiatives in the swedish and polish hotel industries—survey results. *International Journal of Hospitality Management.* 25(4) pp.662-682.

Booth, C. (1989) History of coeliac disease. *BMJ: British Medical Journal.* 298(6672) pp.527.

Borghini, R., Di Tola, M., Salvi, E., Isonne, C., Puzzono, M., Marino, M., Donato, G. & Picarelli, A. (2016) Impact of gluten-free diet on quality of life in celiac patients. *Acta Gastro-Enterologica Belgica.* 79(2) pp.447-453.

Boundouki, G., Humphris, G. & Field, A. (2004) Knowledge of oral cancer, distress and screening intentions: Longer term effects of a patient information leaflet. *Patient Education and Counseling.* 53(1) pp.71-77.

Bowling, A. (2005) Mode of questionnaire administration can have serious effects on data quality. *Journal of Public Health (Oxford, England).* 27(3) pp.281-291.

Brace, I. (2008) *Questionnaire Design: How to Plan, Structure and Write Survey Material for Effective Market Research.* Kogan Page Publishers.

Brar, P., Kwon, G., Egbuna, I., Holleran, S., Ramakrishnan, R., Bhagat, G. & Green, P. (2007) Lack of correlation of degree of villous atrophy with severity of clinical presentation of coeliac disease. *Digestive and Liver Disease.* 39(1) pp.26-29.

Briani, C., Zara, G., Alaedini, A., Grassivaro, F., Ruggero, S., Toffanin, E., Albergoni, M.P., Luca, M., Giometto, B. & Ermani, M. (2008) Neurological complications of celiac disease and autoimmune mechanisms: A prospective study. *Journal of Neuroimmunology.* 195(1-2) pp.171-175.

Bringer, J.D., Johnston, L.H. & Brackenridge, C.H. (2004) Maximizing transparency in a doctoral thesis1: The complexities of writing about the use of QSR* NVIVO within a grounded theory study. *Qualitative Research.* 4(2) pp.247-265.

Brinkmann, S. (2014) Interview. In: Anonymous Springer. pp.1008-1010.

Britten, N. (1995) Qualitative interviews in medical research. *BMJ (Clinical Research Ed.).* 311(6999) pp.251-253.

Brocchi, E., Tomassetti, P., Misitano, B., Epifanio, G., Corinaldesi, R., Bonvicini, F., Gasbarrini, G. & Corazza, G. (2002) Endoscopic markers in adult coeliac disease. *Digestive and Liver Disease.* 34(3) pp.177-182.

Brodie, K., Abel, G. & Burt, J. (2016) Language spoken at home and the association between ethnicity and doctor-patient communication in primary care: Analysis of survey data for south asian and white british patients. *BMJ Open.* 6(3) pp.e010042-2015-010042.

Brown, I., Mino-Kenudson, M., Deshpande, V. & Lauwers, G.Y. (2006) Intraepithelial lymphocytosis in architecturally preserved proximal small intestinal mucosa: An increasing diagnostic problem with a wide differential diagnosis. *Archives of Pathology & Laboratory Medicine.* 130(7) pp.1020-1025.

Bruce, T., Byrne, F. & Kemp, L. (2018) Using skype to support remote clinical supervision for health professionals delivering a sustained maternal early childhood programme: A phenomenographical study. *Contemporary Nurse.* 54(1) pp.4-12.

Brusco, N.K. & Watts, J.J. (2015) Empirical evidence of recall bias for primary health care visits. *BMC Health Services Research.* 15(1) pp.381.

Bryman, A. (2003) *Quantity and Quality in Social Research.* Routledge.

Bull, S.S., McFarlane, M. & King, D. (2001) Barriers to STD/HIV prevention on the internet. *Health Education Research.* 16(6) pp.661-670.

Burden, M., Mooney, P.D., Blanshard, R.J., White, W.L., Cambray-Deakin, D.R. & Sanders, D.S. (2015) Cost and availability of gluten-free food in the UK: In store and online. *Postgraduate Medical Journal.* 91(1081) pp.622-626.

Bures, J. (2018) History of celiac disease. *Vnitrni Lekarstvi.* 64(6) pp.600-601.

Burger, J.P., de Brouwer, B., IntHout, J., Wahab, P.J., Tummers, M. & Drenth, J.P. (2017) Systematic review with meta-analysis: Dietary adherence influences normalization of health-related quality of life in coeliac disease. *Clinical Nutrition.* 36(2) pp.399-406.

Burke, L.A. & Miller, M.K. (2001) Phone interviewing as a means of data collection: Lessons learned and practical recommendations. In: *Forum Qualitative Sozialforschung/Forum: Qualitative Social Research.*

Burnard, P. (1994) The telephone interview as a data collection method. *Nurse Education Today.* 14(1) pp.67-72.

Bushara, K.O., Goebel, S.U., Shill, H., Goldfarb, L.G. & Hallett, M. (2001) Gluten sensitivity in sporadic and hereditary cerebellar ataxia. *Annals of Neurology.* 49(4) pp.540-543.

Butterworth, J.R., Banfield, L.M., Iqbal, T.H. & Cooper, B.T. (2004) Factors relating to compliance with a gluten-free diet in patients with coeliac disease: Comparison of white caucasian and south asian patients. *Clinical Nutrition (Edinburgh, Scotland).* 23(5) pp.1127-1134.

Butterworth, J.R., Iqbal, T.H. & Cooper, B.T. (2005) Coeliac disease in south asians resident in britain: Comparison with white caucasian coeliac patients. *European Journal of Gastroenterology & Hepatology.* 17(5) pp.541-545.

CA, 2. (2015) *Coeliac Australia.* Available at: http://www.coeliac.org.au/ . (Accessed: 19 February 2019).

Cachia, M. & Millward, L. (2011) The telephone medium and semi-structured interviews: A complementary fit. *Qualitative Research in Organizations and Management: An International Journal.* 6(3) pp.265-277.

Camarca, M.E., Mozzillo, E., Nugnes, R., Zito, E., Falco, M., Fattorusso, V., Mobilia, S., Buono, P., Valerio, G. & Troncone, R. (2012) Celiac disease in type 1 diabetes mellitus. *Italian Journal of Pediatrics.* 38(1) pp.10.

Cammarota, G., Cesaro, P., Martino, A., Zuccala, G., Cianci, R., Nista, E., Larocca, L.M., Vecchio, F.M., Gasbarrini, A. & Gasbarrini, G. (2006) High accuracy and cost-effectiveness of a biopsy-avoiding endoscopic approach in diagnosing coeliac disease. *Alimentary Pharmacology & Therapeutics.* 23(1) pp.61-69.

Cammarota, G., Cuoco, L., Cianci, R., Pandolfi, F. & Gasbarrini, G. (2000) Onset of coeliac disease during treatment with interferon for chronic hepatitis C. *The Lancet.* 356(9240) pp.1494-1495.

Campaign (2016) *Coeiacc UK. Campaign to Protect Prescription Services in England.* Available at: https://www.coeliac.org.uk/campaigns-and-research/campaigning-on-health/campaign-to-protect-prescription-services-in-england/ . (Accessed: 19 February 2019).

Canavan, C., Card, T. & West, J. (2014) The incidence of other gastroenterological disease following diagnosis of irritable bowel syndrome in the UK: A cohort study. *PloS One.* 9(9) pp.e106478.

Canova, C., Pitter, G., Zanier, L., Simonato, L., Michaelsson, K. & Ludvigsson, J.F. (2018) Risk of fractures in youths with celiac Disease—A population-based study. *The Journal of Pediatrics.* 198pp.117-120.

Capriles, V.D., Martini, L.A. & Arêas, J.A.G. (2009) Metabolic osteopathy in celiac disease: Importance of a gluten-free diet. *Nutrition Reviews.* 67(10) pp.599-606.

Carr, E.C. & Worth, A. (2001) The use of the telephone interview for research. *Nursing Times Research.* 6(1) pp.511-524.

Caruso, R., Marafini, I., Blanco, G.D.V., Fina, D., Paoluzi, O.A., Colantoni, A., Sedda, S., Pallone, F. & Monteleone, G. (2014) Sampling of proximal and distal duodenal biopsies in the diagnosis and monitoring of celiac disease. *Digestive and Liver Disease.* 46(4) pp.323-329.

Casanova, J. (2007) Immigration and the new religious pluralism: A european union/united states comparison. *Democracy and the New Religious Pluralism.* pp.59-83.

Case, S. (2005) The gluten-free diet: How to provide effective education and resources. *Gastroenterology.* 128(4) pp.S128-S134.

Casella, S., Zanini, B., Lanzarotto, F., Villanacci, V., Ricci, C. & Lanzini, A. (2012) Celiac disease in elderly adults: Clinical, serological, and histological characteristics and the effect of a Gluten-Free diet. *Journal of the American Geriatrics Society.* 60(6) pp.1064-1069.

Casellas, F., Vivancos, J.L. & Malagelada, J. (2006) Current epidemiology and accessibility to diet compliance in adult celiac disease. *Revista Espanola De Enfermedades Digestivas.* 98(6) pp.408.

Casellas, F., Rodrigo, L., Lucendo, A.J., Molina-Infante, J., Vivas, S., Rosinach, M., Dueñas, C. & López-Vivancos, J. (2015) Benefit on health-related quality of life of adherence to gluten-free diet in adult patients with celiac disease. *Revista Española De Enfermedades Digestivas.* 107(4) pp.196-201.

Castro, P.D., Harkin, G., Hussey, M., Christopher, B., Kiat, C., Chin, J.L., Trimble, V., McNamara, D., MacMathuna, P. & Egan, B. (2017) Changes in presentation of celiac disease in ireland from the 1960s to 2015. *Clinical Gastroenterology and Hepatology.* 15(6) pp.864-871. e3.

Catassi, C., Fabiani, E., Rätsch, I., Coppa, G., Giorgi, P., Pierdomenico, R., Alessandrini, S., Iwanejko, G., Domenici, R. & Mei, E. (1996) The coeliac iceberg in italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. *Acta Paediatrica.* 85(s412) pp.29-35.

Catassi, C., Bearzi, I. & Holmes, G.K. (2005) Association of celiac disease and intestinal lymphomas and other cancers. *Gastroenterology.* 128(4) pp.S79-S86.

Catassi, C. & Fasano, A. (2010) Celiac disease diagnosis: Simple rules are better than complicated algorithms. *The American Journal of Medicine.* 123(8) pp.691-693.

Catassi, C., Fabiani, E., Iacono, G., D'Agate, C., Francavilla, R., Biagi, F., Volta, U., Accomando, S., Picarelli, A., De Vitis, I., Pianelli, G., Gesuita, R., Carle, F., Mandolesi, A., Bearzi, I. & Fasano, A. (2007) A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. *The American Journal of Clinical Nutrition.* 85(1) pp.160-166.

Catassi, C., Gatti, S. & Fasano, A. (2014) The new epidemiology of celiac disease. *Journal of Pediatric Gastroenterology and Nutrition.* 59 Suppl 1pp.S7-9.

Cavell, B., Stenhammar, L., Ascher, H., Danielsson, L., Dannaeus, A., Lindberg, T. & Lindquist, B. (1992) Increasing incidence of childhood coeliac disease in sweden. results of a national study. *Acta Paediatrica.* 81(8) pp.589-592.

Cawthon, P.M. (2011) Gender differences in osteoporosis and fractures. *Clinical Orthopaedics and Related Research®.* 469(7) pp.1900-1905.

CCG Dudley (2018) *Prescribing of Gluten Free Products on NHS Prescriptions in Dudley.* Available at: http://www.dudleyccg.nhs.uk/prescribing-of-gluten-free-products-on-nhs-prescriptions-in-dudley/ . (Accessed: 19 February 2019).

Cellier, C., Delabesse, E., Helmer, C., Patey, N., Matuchansky, C., Jabri, B., Macintyre, E., Cerf-Bensussan, N., Brousse, N. & French Coeliac Disease Study Group (2000a) Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. *The Lancet.* 356(9225) pp.203-208.

Cellier, C., Flobert, C., Cormier, C., Roux, C. & Schmitz, J. (2000b) Severe osteopenia in symptom-free adults with a childhood diagnosis of coeliac disease. *Lancet.* 355(9206) pp.806.

Chander, U., Leeman-Neill, R.J. & Bhagat, G. (2018) Pathogenesis of enteropathy-associated T cell lymphoma. *Current Hematologic Malignancy Reports.* pp.1-10.

Chang, L. & Krosnick, J.A. (2009) National surveys via RDD telephone interviewing versus the internet: Comparing sample representativeness and response quality. *Public Opinion Quarterly.* 73(4) pp.641-678.

Chapple, A. (1999) The use of telephone interviewing for qualitiative research. *Nurse Researcher.* 6(3) pp.85.

Charalampopoulos, D., Panayiotou, J., Chouliaras, G., Zellos, A., Kyritsi, E. & Roma, E. (2013) Determinants of adherence to gluten-free diet in greek children with coeliac disease: A cross-sectional study. *European Journal of Clinical Nutrition.* 67(6) pp.615-619.

Chaudhuri, A. & Behan, P.O. (2004) Fatigue in neurological disorders. *The Lancet.* 363(9413) pp.978-988.

Chauhan, J., Kumar, P., Dutta, A., Basu, S. & Kumar, A. (2010) Assessment of dietary compliance to gluten free diet and psychosocial problems in indian children with celiac disease. *The Indian Journal of Pediatrics.* 77(6) pp.649-654.

Chen, X., Hnida, K., Graewert, M.A., Andersen, J.T., Iversen, R., Tuukkanen, A., Svergun, D. & Sollid, L.M. (2015) Structural basis for antigen recognition by transglutaminase 2-specific autoantibodies in celiac disease. *The Journal of Biological Chemistry.* 290(35) pp.21365-21375.

Chin, R.L., Sander, H.W., Brannagan, T.H., Green, P.H., Hays, A.P., Alaedini, A. & Latov, N. (2003) Celiac neuropathy. *Neurology.* 60(10) pp.1581-1585.

Choudhary, G., Gupta, R.K. & Beniwal, J. (2017) Bone mineral density in celiac disease. *The Indian Journal of Pediatrics.* 84(5) pp.344-348.

Chow, M.A., Lebwohl, B., Reilly, N.R. & Green, P.H. (2012) Immunoglobulin A deficiency in celiac disease. *Journal of Clinical Gastroenterology.* 46(10) pp.850-854.

Chung, M.L., Moser, D.K., Lennie, T.A., Worrall-Carter, L., Bentley, B., Trupp, R. & Armentano, D.S. (2006) Gender differences in adherence to the sodium-restricted diet in patients with heart failure. *Journal of Cardiac Failure.* 12(8) pp.628-634.

Ciacci, C., D'agate, C., De Rosa, A., Franzese, C., Errichiello, S., Gasperi, V., Pardi, A., Quagliata, D., Visentini, S. & Greco, L. (2003a) Self-rated quality of life in celiac disease. *Digestive Diseases and Sciences.* 48(11) pp.2216-2220.

Ciacci, C., Iavarone, A., Mazzacca, G. & De Rosa, A. (1998a) Depressive symptoms in adult coeliac disease. *Scandinavian Journal of Gastroenterology.* 33(3) pp.247-250.

Ciacci, C., Cirillo, M., Cavallaro, R. & Mazzacca, G. (2002) Long-term follow-up of celiac adults on gluten-free diet: Prevalence and correlates of intestinal damage. *Digestion.* 66(3) pp.178-185.

Ciacci, C., D'Agate, C., De Rosa, A., Franzese, C., Errichiello, S., Gasperi, V., Pardi, A., Quagliata, D., Visentini, S. & Greco, L. (2003b) Self-rated quality of life in celiac disease. *Digestive Diseases and Sciences.* 48(11) pp.2216-2220.

Ciacci, C., Iavarone, A., Mazzacca, G. & De Rosa, A. (1998b) Depressive symptoms in adult coeliac disease. *Scandinavian Journal of Gastroenterology.* 33(3) pp.247-250.

Cicarelli, G., Della Rocca, G., Amboni, M., Ciacci, C., Mazzacca, G., Filla, A. & Barone, P. (2003) Clinical and neurological abnormalities in adult celiac disease. *Neurological Sciences.* 24(5) pp.311-317.

Ciclitira, P., Dewar, D. & et al (2010) *Incdence of Coeliac Disease British Society of Gastroenterology. BSG.*

Ciclitira, P.J. & Ellis, H.J. (1987) Investigation of cereal toxicity in coeliac disease. *Postgraduate Medical Journal.* 63(743) pp.767-775.

Clark, R.A., Inglis, S.C., McAlister, F.A., Cleland, J.G. & Stewart, S. (2007) Telemonitoring or structured telephone support programmes for patients with chronic heart failure: Systematic review and meta-analysis. *BMJ (Clinical Research Ed.).* 334(7600) pp.942.

Coeliac UK (2018) *The Gluten Free Diet.* Available at: https://www.coeliac.org.uk/gluten-free-diet-and-lifestyle/gf-diet/ . (Accessed: 19 February 2019).

Coeliac UK (2016a) *Eating Out.* Available at: https://www.coeliac.org.uk/gluten-free-diet-and-lifestyle/eating-out/ (Accessed: 19 February 2019).

Coeliac UK (2016b) *Food Labels.* Available at: https://www.coeliac.org.uk/gluten-free-diet-and-lifestyle/food-shopping/food-labels/ . (Accessed: 19 February 2019).

Coeliac UK (2016c) *Gluten-Free Products and Services.* Available at: https://www.coeliac.org.uk/gluten-free-diet-and-lifestyle/gluten-free-products/ . (Accessed: 19 February 2019).

Coeliac UK (2015) *Gluten Sensitivity.* Available at: https://www.coeliac.org.uk/coeliac-disease/about-coeliac-disease-and-dermatitis-herpetiformis/gluten-sensitivity/ . (Accessed: 19 February 2019).

Cohen, S.M. (2009) Concept analysis of adherence in the context of cardiovascular risk reduction. In: *Nursing Forum.* Wiley Online Library. pp.25-36.

Collier, R. (2011) Educating patients with pictures. *CMAJ : Canadian Medical Association Journal = Journal De L'Association Medicale Canadienne.* 183(15) pp.E1094-3967. Epub 2011 Sep 12.

Collin, P., Vilppula, A., Luostarinen, L., Holmes, G. & Kaukinen, K. (2018) Coeliac disease in later life must not be missed. *Alimentary Pharmacology & Therapeutics.*

Collin, P., Salmi, T.T., Hervonen, K., Kaukinen, K. & Reunala, T. (2017) Dermatitis herpetiformis: A cutaneous manifestation of coeliac disease. *Annals of Medicine.* 49(1) pp.23-31.

Collin, P., Reunala, T., Pukkala, E., Laippala, P., Keyrilainen, O. & Pasternack, A. (1994) Coeliac disease--associated disorders and survival. *Gut.* 35(9) pp.1215-1218.

Colombo, E., Cermesoni, L. & Morganti, D. (2003) Celiac sprue: Another autoimmune syndrome associated with hepatitis C? *Digestive and Liver Disease.* 1(35) pp.64-65.

Comino, I., Fernández-Bañares, F., Esteve, M., Ortigosa, L., Castillejo, G., Fambuena, B., Ribes-Koninckx, C., Sierra, C., Rodríguez-Herrera, A. & Salazar, J.C. (2016) Fecal gluten peptides reveal limitations of serological tests and food questionnaires for monitoring gluten-free diet in celiac disease patients. *The American Journal of Gastroenterology.* 111(10) pp.1456.

Comino, I., Real, A., Vivas, S., Siglez, M.A., Caminero, A., Nistal, E., Casqueiro, J., Rodriguez-Herrera, A., Cebolla, A. & Sousa, C. (2012) Monitoring of gluten-free diet compliance in celiac patients by assessment of gliadin 33-mer equivalent epitopes in feces. *The American Journal of Clinical Nutrition.* 95(3) pp.670-677.

Cook, C., Heath, F. & Thompson, R.L. (2000) A meta-analysis of response rates in web-or internet-based surveys. *Educational and Psychological Measurement.* 60(6) pp.821-836.

Cooke, W. & Smith, W.T. (1966) Neurological disorders associated with adult celiac disease. *Brain.* 89(4) pp.683-722.

Cooper, S., Kennedy, N., Mohamed, B., Abuzakouk, M., Dunne, J., Byrne, G., McDonald, G., Davies, A., Edwards, C. & Kelly, J. (2013) Immunological indicators of coeliac disease activity are not altered by long-term oats challenge. *Clinical & Experimental Immunology.* 171(3) pp.313-318.

Corazza, G.R., Brusco, G., Andreani, M., Biagi, F., Di Stefano, M. & Gasbarrini, G. (1996) Previous misdiagnosis and diagnostic delay in adult celiac sprue. *Journal of Clinical Gastroenterology.* 22(4) pp.324-325.

Corazza, G.R., Di Sario, A., Cecchetti, L., Tarozzi, C., Corrao, G., Bernardi, M. & Gasbarrini, G. (1995) Bone mass and metabolism in patients with celiac disease. *Gastroenterology.* 109(1) pp.122-128.

Corazza, G., Valentini, R.A., Frisoni, M., Volta, U., Corrao, G., Bianchi, F.B. & Gasbarrini, G. (1992) Gliadin immune reactivity is associated with overt and latent enteropathy in relatives of celiac patients. *Gastroenterology.* 103(5) pp.1517-1522.

Corney, R.H. (1990) Sex differences in general practice attendance and help seeking for minor illness. *Journal of Psychosomatic Research.* 34(5) pp.525-534.

Corrao, G., Corazza, G.R., Bagnardi, V., Brusco, G., Ciacci, C., Cottone, M., Guidetti, C.S., Usai, P., Cesari, P. & Pelli, M.A. (2001) Mortality in patients with coeliac disease and their relatives: A cohort study. *The Lancet.* 358(9279) pp.356-361.

Cosnes, J., Cosnes, C., Cosnes, A., Contou, J., Reijasse, D., Carbonnel, F., Beaugerie, L. & Gendre, J. (2002) Undiagnosed celiac disease in childhood. *Gastroenterologie Clinique Et Biologique.* 26(6-7) pp.616-623.

Cossu, G., Carta, M.G., Contu, F., Mela, Q., Demelia, L., Elli, L. & Dell'Osso, B. (2017) Coeliac disease and psychiatric comorbidity: Epidemiology, pathophysiological mechanisms, quality-of-life, and gluten-free diet effects. *International Review of Psychiatry.* 29(5) pp.489-503.

Cote, R.A. & Robboy, S. (1980) Progress in medical information management: Systematized nomenclature of medicine (SNOMED). *Jama.* 243(8) pp.756-762.

Coughlan, M., Cronin, P. & Ryan, F. (2009) Survey research: Process and limitations. *International Journal of Therapy & Rehabilitation.* 16(1) .

Coughlin, S.S. (1990) Recall bias in epidemiologic studies. *Journal of Clinical Epidemiology.* 43(1) pp.87-91.

Coulter, A. (1998) Evidence based patient information is important, so there needs to be a national strategy to ensure it. *British Medical Journal.* 317(7153) pp.225-227.

Coulter, A. & Ellins, J. (2007) Effectiveness of strategies for informing, educating, and involving patients. *BMJ (Clinical Research Ed.).* 335(7609) pp.24-27.

Counihan, C. & Van Esterik, P. (2012) Food and culture: A reader. In: Anonymous Routledge. pp.107-231.

Cranney, A., Zarkadas, M., Graham, I.D., Butzner, J.D., Rashid, M., Warren, R., Molloy, M., Case, S., Burrows, V. & Switzer, C. (2007) The canadian celiac health survey. *Digestive Diseases and Sciences.* 52(4) pp.1087-1095.

Crawford, J.R. & Henry, J.D. (2003) The depression anxiety stress scales (DASS): Normative data and latent structure in a large non-clinical sample. *British Journal of Clinical Psychology.* 42(2) pp.111-131.

Crawford, M.J., Rutter, D., Manley, C., Weaver, T., Bhui, K., Fulop, N. & Tyrer, P. (2002) Systematic review of involving patients in the planning and development of health care. *BMJ (Clinical Research Ed.).* 325(7375) pp.1263.

Crocker, H., Jenkinson, C. & Peters, M. (2018a) Quality of life in coeliac disease: Item reduction, scale development and psychometric evaluation of the coeliac disease assessment questionnaire (CDAQ). *Alimentary Pharmacology & Therapeutics.*

Crocker, H., Jenkinson, C. & Peters, M. (2018b) Quality of life in coeliac disease: Qualitative interviews to develop candidate items for the coeliac disease assessment questionnaire. *Patient Related Outcome Measures.* 9pp.211.

Crocker, H., Peters, M. & Jenkinson, C. (2013) Quality of life in coeliac disease: The qualitative development of a new patient-reported outcome measure. In: *Quality of Life Research.* SPRINGER VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS.

Cronin, C.C., Feighery, A., Ferriss, J.B., Liddy, C., Shanahah, F. & Feighery, C. (1997) High prevalence of celiac disease among patients with insulin-dependent (type I) diabetes mellitus. *American Journal of Gastroenterology.* 92(12) pp.2210-2212.

Cronin, O., Flanagan, E. & Dowling, D. (2018) Coeliac disease in the modern era: Severity of small bowel mucosal injury at diagnosis with analysis of clinical correlates and rate of improvement on a gluten free diet. *World Journal of Gastrointestinal Pharmacology and Therapeutics.* 9(6) pp.55.

CSUK, 2. (2016) *Mobile Phone App for Patients with Coeliac Disease.* Available at: https://www.coeliac.org.uk/gluten-free-diet-and-lifestyle/mobile-phone-app/ . (Accessed: 19 February 2019).

Cummings, S.M., Savitz, L.A. & Konrad, T.R. (2001) Reported response rates to mailed physician questionnaires. *Health Services Research.* 35(6) pp.1347-1355.

Cummins, A.G. & Roberts-Thomson, I.C. (2009) Prevalence of celiac disease in the Asia–Pacific region. *Journal of Gastroenterology and Hepatology.* 24(8) pp.1347-1351.

Curtin, R., Presser, S. & Singer, E. (2000) The effects of response rate changes on the index of consumer sentiment. *Public Opinion Quarterly.* 64(4) pp.413-428.

Czaja-Bulsa, G. (2015) Non coeliac gluten sensitivity–A new disease with gluten intolerance. *Clinical Nutrition.* 34(2) pp.189-194.

Czaja-Bulsa, G. & Bulsa, M. (2018) Adherence to gluten-free diet in children with celiac disease. *Nutrients.* 10(10) pp.1424.

Da Silva, G.F., Morano, M.T.A., Sales, M.P.U., Olegário, N.B., Cavalcante, A.G.M. & Pereira, E.D. (2014) Comparison of face-to-face interview and telephone interview administration of COPD assessment test: A randomized study. *Quality of Life Research.* 23(4) pp.1193-1197.

Dahele, A. & Ghosh, S. (2001) Vitamin B12 deficiency in untreated celiac disease. *The American Journal of Gastroenterology.* 96(3) pp.745-750.

Dalgic, B., Sari, S., Basturk, B., Ensari, A., Egritas, O., Bukulmez, A. & Baris, Z. (2011) Prevalence of celiac disease in healthy turkish school children. *The American Journal of Gastroenterology.* 106(8) pp.1512.

Dang, B.N., Westbrook, R.A., Njue, S.M. & Giordano, T.P. (2017) Building trust and rapport early in the new doctor-patient relationship: A longitudinal qualitative study. *BMC Medical Education.* 17(1) pp.32.

Das, P., Gahlot, G.P., Singh, A., Baloda, V., Rawat, R., Verma, A.K., Khanna, G., Roy, M., George, A., Singh, A., Nalwa, A., Ramteke, P., Yadav, R., Ahuja, V., Sreenivas, V., Gupta, S.D. & Makharia, G.K. (2019) Quantitative histology-based classification system for assessment of the intestinal mucosal histological changes in patients with celiac disease. Intestinal Research.De Vincenzi, M., Luchetti, R., Peruffo, A.D., Curioni, A., Pogna, N.E. & Gasbarrini, G. (1996) In vitro assessment of acetic-acid-soluble proteins (glutenin) toxicity in celiac disease. Journal of Biochemical Toxicology. 11(4) pp.205-210.

Deakin, T., Cade, J., Williams, R. & Greenwood, D. (2006) Structured patient education: The diabetes X-PERT programme makes a difference. *Diabetic Medicine.* 23(9) pp.944-954.

Deepak, C., Berry, N., Vaiphei, K., Dhaka, N., Sinha, S.K. & Kochhar, R. (2018) Quality of life in celiac disease and the effect of gluten-free diet. *JGH Open: An Open Access Journal of Gastroenterology and Hepatology.* 2(4) pp.124.

DeGaetani, M., Tennyson, C.A., Lebwohl, B., Lewis, S.K., Daya, H.A., Arguelles-Grande, C., Bhagat, G. & Green, P.H. (2013) Villous atrophy and negative celiac serology: A diagnostic and therapeutic dilemma. *The American Journal of Gastroenterology.* 108(5) pp.647.

Denery-Papini, S., Nicolas, Y. & Popineau, Y. (1999) Efficiency and limitations of immunochemical assays for the testing of gluten-free foods. *Journal of Cereal Science.* 30(2) pp.121-131.

Dennis, M. & Case, S. (2004) Going gluten-free: A primer for clinicians. *Practical Gastroenterology.* 28(4) pp.86-105.

Denscombe, M. (2009) Item non-response rates: A comparison of online and paper questionnaires. *International Journal of Social Research Methodology.* 12(4) pp.281-291.

Department of Health and Social Care (2018) *Responses to the Consultation on the Gluten-Free Food Regulation.* Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/753733/responses-to-the-consultation-on-gluten-free-food-regulations.pdf . (Accessed: 19 February 2019).

Desimone, L. (2011) Outcomes: Content-focused learning improves teacher practice and student results. *Journal of Staff Development.* 32(4) .

Desroches, S., Lapointe, A., Ratté, S., Gravel, K., Légaré, F., Njaya, M. & Payne, A. (2010) Interventions to enhance adherence to dietary advice for preventing and managing chronic diseases in adults. *Cochrane Database of Systematic Reviews.* 9.

Dewar, D.H. & Ciclitira, P.J. (2005) Clinical features and diagnosis of celiac disease. *Gastroenterology.* 128(4) pp.S19-S24.

Dewar, D.H., Donnelly, S.C., McLaughlin, S.D., Johnson, M.W., Ellis, H.J. & Ciclitira, P.J. (2012) Celiac disease: Management of persistent symptoms in patients on a gluten-free diet. *World Journal of Gastroenterology : WJG.* 18(12) pp.1348-1356.

Di Sabatino, A. & Corazza, G.R. (2009) Coeliac disease. *The Lancet.* 373(9673) pp.1480-1493.

Di Sabatino, A. & Corazza, G.R. (2013) Some clarification is necessary on the oslo definitions for coeliac disease-related terms. *Gut.* 62(1) pp.182-2012-302613. Epub 2012 Jun 26.

Di Stefano, M., Veneto, G., Corrao, G. & Corazza, G.R. (2000) Role of lifestyle factors in the pathogenesis of osteopenia in adult coeliac disease: A multivariate analysis. *European Journal of Gastroenterology & Hepatology.* 12(11) pp.1195-1199.

DiCicco-Bloom, B. & Crabtree, B.F. (2006) The qualitative research interview. *Medical Education.* 40(4) pp.314-321.

Dicke, W.K. (1950) *Coeliac Disease.Investigation of the Harmful Effects of Certain Types of Cereal on Patients with Coeliac Disease.*

Dicke, W.K. (1941) Simple dietary treatment for the syndrome of GheeHerter. ned tijdschr geneeskd. In: Anonymous pp.85-1715.

Dickey, W., Hughes, D.F. & McMillan, S.A. (2000) Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery. *The American Journal of Gastroenterology.* 95(3) pp.712.

Dickinson, D., Raynor, D.K. & Duman, M. (2001) Patient information leaflets for medicines: Using consumer testing to determine the most effective design. *Patient Education and Counseling.* 43(2) pp.147-159.

Dieterich, W., Laag, E., Schöpper, H., Volta, U., Ferguson, A., Gillett, H., Riecken, E.O. & Schuppan, D. (1998) Autoantibodies to tissue transglutaminase as predictors of celiac disease. *Gastroenterology.* 115(6) pp.1317-1321.

DiGiacomo, D.V., Tennyson, C.A., Green, P.H. & Demmer, R.T. (2013) Prevalence of gluten-free diet adherence among individuals without celiac disease in the USA: Results from the continuous national health and nutrition examination survey 2009–2010. *Scandinavian Journal of Gastroenterology.* 48(8) pp.921-925.

Dillman, D.A., Sinclair, M.D. & Clark, J.R. (1993) Effects of questionnaire length, respondent-friendly design, and a difficult question on response rates for occupant-addressed census mail surveys. *Public Opinion Quarterly.* 57(3) pp.289-304.

DiMatteo, M.R. (2004) Variations in patients' adherence to medical recommendations: A quantitative review of 50 years of research. *Medical Care.* 42(3) pp.200-209.

Dipper, C., Maitra, S., Thomas, R., Lamb, C., MCLEAN-TOOKE, A., Ward, R., Smith, D., Spickett, G. & Mansfield, J. (2009) Anti-tissue transglutaminase antibodies in the follow-up of adult coeliac disease. *Alimentary Pharmacology & Therapeutics.* 30(3) pp.236-244.

Dixit, R., Lebwohl, B., Ludvigsson, J.F., Lewis, S.K., Rizkalla-Reilly, N. & Green, P.H. (2014) Celiac disease is diagnosed less frequently in young adult males. *Digestive Diseases and Sciences.* 59(7) pp.1509-1512.

Dolcino, M., Zanoni, G., Bason, C., Tinazzi, E., Boccola, E., Valletta, E., Contreas, G., Lunardi, C. & Puccetti, A. (2013) A subset of anti-rotavirus antibodies directed against the viral protein VP7 predicts the onset of celiac disease and induces typical features of the disease in the intestinal epithelial cell line T84. *Immunologic Research.* 56(2-3) pp.465-476.

Donaldson, M.R., Book, L.S., Leiferman, K.M., Zone, J.J. & Neuhausen, S.L. (2008) Strongly positive tissue transglutaminase antibodies are associated with marsh 3 histopathology in adult and pediatric celiac disease. *Journal of Clinical Gastroenterology.* 42(3) pp.256-260.

Dowd, A.J., Jackson, C., Tang, K.T., Nielsen, D., Clarkin, D.H. & Culos-Reed, S.N. (2018) MyHealthyGut: Development of a theory-based self-regulatory app to effectively manage celiac disease. *mHealth.* 4(6) .

Dowd, A., Tamminen, K., Jung, M., Case, S., McEwan, D. & Beauchamp, M. (2014) Motives for adherence to a gluten-free diet: A qualitative investigation involving adults with coeliac disease. *Journal of Human Nutrition and Dietetics.* 27(6) pp.542-549.

Downey, L., Houten, R., Murch, S. & Longson, D. (2015) Recognition, assessment, and management of coeliac disease: Summary of updated NICE guidance. *Bmj.* 351pp.h4513.

Drossman, D.A., Morris, C.B., Schneck, S., Hu, Y.J., Norton, N.J., Norton, W.F., Weinland, S.R., Dalton, C., Leserman, J. & Bangdiwala, S.I. (2009) International survey of patients with IBS: Symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit. *Journal of Clinical Gastroenterology.* 43(6) pp.541-550.

Du, Y., Shan, L.F., Cao, Z.Z., Feng, J.C. & Cheng, Y. (2017) Prevalence of celiac disease in patients with down syndrome: A meta-analysis. *Oncotarget.* 9(4) pp.5387-5396.

Dubé, C., Rostom, A., Sy, R., Cranney, A., Saloojee, N., Garritty, C., Sampson, M., Zhang, L., Yazdi, F. & Mamaladze, V. (2005) The prevalence of celiac disease in average-risk and at-risk western european populations: A systematic review. *Gastroenterology.* 128(4) pp.S57-S67.

Dudeja, P., Dudeja, A., Singh, G. & Mukherji, S. (2016) Regulatory framework for" gluten-free" foods in india: Magic bullet for celiac disease patients. *Medical Journal of Dr.DY Patil University.* 9(6) pp.680.

Duggan, J. & Duggan, A. (2005) Systematic review: The liver in coeliac disease. *Alimentary Pharmacology & Therapeutics.* 21(5) pp.515-518.

DuPont, F.M., Chan, R., Lopez, R. & Vensel, W.H. (2005) Sequential extraction and quantitative recovery of gliadins, glutenins, and other proteins from small samples of wheat flour. *Journal of Agricultural and Food Chemistry.* 53(5) pp.1575-1584.

Durante-Mangoni, E., Iardino, P., Resse, M., Cesaro, G., Sica, A., Farzati, B., Ruggiero, G. & Adinolfi, L.E. (2004) Silent celiac disease in chronic hepatitis C: Impact of interferon treatment on the disease onset and clinical outcome. *Journal of Clinical Gastroenterology.* 38(10) pp.901-905.

Dyer, O. (2003) Patients will be reminded of appointments by text messages. *BMJ (Clinical Research Ed.).* 326(7402) pp.1281-a.

Eakin, E.G., Lawler, S.P., Vandelanotte, C. & Owen, N. (2007) Telephone interventions for physical activity and dietary behavior change: A systematic review. *American Journal of Preventive Medicine.* 32(5) pp.419-434.

East Leicestershire and Rutland CCG (2016) ***Gluten-Free**.* Available at: https://eastleicestershireandrutlandccg.nhs.uk/yourhealth/prescriptions/gluten-free/ . (Accessed: 19 February 2019).

Edwards, P., Roberts, I., Sandercock, P. & Frost, C. (2004) Follow-up by mail in clinical trials: Does questionnaire length matter? *Controlled Clinical Trials.* 25(1) pp.31-52.

Edwards, P.J., Roberts, I., Clarke, M.J., Diguiseppi, C., Wentz, R., Kwan, I., Cooper, R., Felix, L.M. & Pratap, S. (2009) Methods to increase response to postal and electronic questionnaires. *The Cochrane Database of Systematic Reviews.* (3):MR000008. doi(3) pp.MR000008.

Efthymakis, K., Serio, M., Milano, A., Laterza, F., Bonitatibus, A., Di Nicola, M. & Neri, M. (2017) Application of the biopsy-sparing ESPGHAN guidelines for celiac disease diagnosis in adults: A real-life study. *Digestive Diseases and Sciences.* 62(9) pp.2433-2439.

Eide, H., Graugaard, P., Holgersen, K. & Finset, A. (2003) Physician communication in different phases of a consultation at an oncology outpatient clinic related to patient satisfaction. *Patient Education and Counseling.* 51(3) pp.259-266.

Eilers, G.M. (2004) Improving patient satisfaction with waiting time. *Journal of American College Health.* 53(1) pp.41-48.

Eisenhower, D., Mathiowetz, N.A. & Morganstein, D. (2004) Recall error: Sources and bias reduction techniques. *Measurement Errors in Surveys.* pp.125-144.

Ekhtiari, S., Kay, J., Simunovic, N., Musahl, V., Peterson, D.C. & Ayeni, O.R. (2017) What makes a successful survey? A systematic review of surveys used in anterior cruciate ligament reconstruction. *Arthroscopy: The Journal of Arthroscopic & Related Surgery.*

Elkin, A., Grant, C., Coleman, T. & Sereika, S.M. (2018) Use of an educational module to improve confidence and knowledge of celiac disease among nurse practitioners in pennsylvania: A quasi-experimental mixed-methods design. *Gastroenterology Nursing.* 41(5) pp.412-423.

Elli, L., Zini, E., Tomba, C., Bardella, M.T., Bosari, S., Conte, D., Runza, L., Roncoroni, L. & Ferrero, S. (2015) Histological evaluation of duodenal biopsies from coeliac patients: The need for different grading criteria during follow-up. *BMC Gastroenterology.* 15(1) pp.133.

Ellis, A. (1981) Coeliac disease: Previous family studies. In: Anonymous Springer. pp.197-200.

Emilsson, L., Carlsson, R., Holmqvist, M., James, S. & Ludvigsson, J.F. (2013) The characterisation and risk factors of ischaemic heart disease in patients with coeliac disease. *Alimentary Pharmacology & Therapeutics.* 37(9) pp.905-914.

Ensari, A. (2016) Coeliac disease: To classify or not to classify–that is the question! *Gastroenterology and Hepatology from Bed to Bench.* 9(2) pp.73-74.

Errichiello, S., Esposito, O., Di Mase, R., Camarca, M.E., Natale, C., Limongelli, M.G., Marano, C., Coruzzo, A., Lombardo, M., Strisciuglio, P. & Greco, L. (2010) Celiac disease: Predictors of compliance with a gluten-free diet in adolescents and young adults. *Journal of Pediatric Gastroenterology and Nutrition.* 50(1) pp.54-60.

Espino, A., Castillo, L.C., Guiraldes, E., Santibanez, H. & Miquel, J.F. (2011) A national online survey applied to patients with celiac disease in chile. *Revista Medica De Chile.* 139(7) pp.841-847.

Estévez, V., Ayala, J., Vespa, C. & Araya, M. (2016) The gluten-free basic food basket: A problem of availability, cost and nutritional composition. *European Journal of Clinical Nutrition.* 70(10) pp.1215.

Evans, K.E., McAllister, R. & Sanders, D.S. (2009) Should we screen for coeliac disease? no. *BMJ (Clinical Research Ed.).* 339pp.b3674.

Evans, M., Robling, M., Maggs Rapport, F., Houston, H., Kinnersley, P. & Wilkinson, C. (2002) It doesn't cost anything just to ask, does it? the ethics of questionnaire-based research. *Journal of Medical Ethics.* 28(1) pp.41-44.

Fabiani, E., Taccari, L.M., Ratsch, I.M., Di Giuseppe, S., Coppa, G.V. & Catassi, C. (2000) Compliance with gluten-free diet in adolescents with screening-detected celiac disease: A 5-year follow-up study. *The Journal of Pediatrics.* 136(6) pp.841-843.

Falcomer, A.L., Santos Araujo, L., Farage, P., Santos Monteiro, J., Yoshio Nakano, E. & Puppin Zandonadi, R. (2018) Gluten contamination in food services and industry: A systematic review. *Critical Reviews in Food Science and Nutrition.* pp.1-15.

Fan, W. & Yan, Z. (2010) Factors affecting response rates of the web survey: A systematic review. *Computers in Human Behavior.* 26(2) pp.132-139.

Farrell, R.J. & Kelly, C.P. (2002) Celiac sprue. *New England Journal of Medicine.* 346(3) pp.180-188.

Farrokhi, F. & Mahmoudi-Hamidabad, A. (2012) Rethinking convenience sampling: Defining quality criteria. *Theory and Practice in Language Studies.* 2(4) pp.784.

Fasano, A. (1996) Where have all the american celiacs gone? *Acta Paediatrica.* 85pp.20-24.

Fasano, A., Berti, I., Gerarduzzi, T., Not, T., Colletti, R.B., Drago, S., Elitsur, Y., Green, P.H., Guandalini, S., Hill, I.D., Pietzak, M., Ventura, A., Thorpe, M., Kryszak, D., Fornaroli, F., Wasserman, S.S., Murray, J.A. & Horvath, K. (2003) Prevalence of celiac disease in at-risk and not-at-risk groups in the united states: A large multicenter study. *Archives of Internal Medicine.* 163(3) pp.286-292.

Faye, A.S., Mahadev, S., Lebwohl, B. & Green, P.H. (2018) Determinants of patient satisfaction in celiac disease care. *Journal of Clinical Gastroenterology.* 52(1) pp.30-35.

Feldman, M., Friedman, L.S. & Brandt, L.J. (2015) *Sleisenger and Fordtran's Gastrointestinal and Liver Disease E-Book: Pathophysiology, Diagnosis, Management.* Elsevier Health Sciences.

Fera, T., Cascio, B., Angelini, G., Martini, S. & Guidetti, C.S. (2003) Affective disorders and quality of life in adult coeliac disease patients on a gluten-free diet. *European Journal of Gastroenterology & Hepatology.* 15(12) pp.1287-1292.

Ferguson, W.J. & Candib, L.M. (2002) Culture, language, and the doctor-patient relationship. *FMCH Publications and Presentations.* pp.61.

Fernandez-Banares, F., Arau, B., Dieli-Crimi, R., Rosinach, M., Nunez, C. & Esteve, M. (2017) Systematic review and meta-analysis show 3% of patients with celiac disease in spain to be negative for HLA-DQ2.5 and HLA-DQ8. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association.* 15(4) pp.594-596.

Flaherty, H. (2014) *Gluten-Free Diet Adherence in Adult Coeliac Disease: Exploring Multiple Perspectives.*

Flick, U. (2009) *An Introduction to Qualitative Research.* Sage.

Flik, C.E., Bakker, L., Laan, W., van Rood, Y.R., Smout, A.J. & de Wit, N.J. (2017) Systematic review: The placebo effect of psychological interventions in the treatment of irritable bowel syndrome. *World Journal of Gastroenterology.* 23(12) pp.2223-2233.

Food and Drug Administration, HHS (2013) Food labeling: Gluten-free labeling of foods. final rule. *Federal Register.* 78(150) pp.47154-47179.

Ford, A.C., Chey, W.D., Talley, N.J., Malhotra, A., Spiegel, B.M. & Moayyedi, P. (2009) Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome: Systematic review and meta-analysis. *Archives of Internal Medicine.* 169(7) pp.651-658.

Fowell, A.J., Thomas, P.W., Surgenor, S.L. & Snook, J.A. (2006) The epidemiology of coeliac disease in east dorset 1993-2002: An assessment of the 'coeliac iceberg', and preliminary evidence of case clustering. *QJM : Monthly Journal of the Association of Physicians.* 99(7) pp.453-460.

Francis, J.J., Johnston, M., Robertson, C., Glidewell, L., Entwistle, V., Eccles, M.P. & Grimshaw, J.M. (2010) What is an adequate sample size? operationalising data saturation for theory-based interview studies. *Psychology and Health.* 25(10) pp.1229-1245.

Franklin, V.L., Waller, A., Pagliari, C. & Greene, S.A. (2006) A randomized controlled trial of sweet talk, a text-messaging system to support young people with diabetes. *Diabetic Medicine.* 23(12) pp.1332-1338.

Frederikson, L.G. & Bull, P.E. (1995) Evaluation of a patient education leaflet designed to improve communication in medical consultations. *Patient Education and Counseling.* 25(1) pp.51-57.

Fry, L., Madden, A. & Fallaize, R. (2018) An investigation into the nutritional composition and cost of gluten-free versus regular food products in the UK. *Journal of Human Nutrition and Dietetics.* 31(1) pp.108-120.

Fueyo-Diaz, R., Gascon-Santos, S., Asensio-Martinez, A., Sanchez-Calavera, M.A. & Magallon-Botaya, R. (2016) Transcultural adaptation and validation of the celiac dietary adherence test. A simple questionnaire to measure adherence to a gluten-free diet. *Revista Espanola De Enfermedades Digestivas : Organo Oficial De La Sociedad Espanola De Patologia Digestiva.* 108(3) pp.138-144.

Gabarron, E., Fernandez-Luque, L., Armayones, M. & Lau, A.Y. (2013) Identifying measures used for assessing quality of YouTube videos with patient health information: A review of current literature. *Interactive Journal of Medical Research.* 2(1) pp.e6.

Galdas, P.M., Cheater, F. & Marshall, P. (2005) Men and health help-seeking behaviour: Literature review. *Journal of Advanced Nursing.* 49(6) pp.616-623.

Galea, S. & Tracy, M. (2007) Participation rates in epidemiologic studies. *Annals of Epidemiology.* 17(9) pp.643-653.

Galesic, M. & Bosnjak, M. (2009) Effects of questionnaire length on participation and indicators of response quality in a web survey. *Public Opinion Quarterly.* 73(2) pp.349-360.

Gallagher, E. (2009) *Gluten-Free Food Science and Technology.* John Wiley & Sons.

Galli, G., Esposito, G., Lahner, E., Pilozzi, E., Corleto, V., Di Giulio, E., Spiriti, A. & Annibale, B. (2014) Histological recovery and gluten-free diet adherence: A prospective 1-year follow-up study of adult patients with coeliac disease. *Alimentary Pharmacology & Therapeutics.* 40(6) pp.639-647.

Garbett, R. & Mccormack, B. (2001) The experience of practice development: An exploratory telephone interview study. *Journal of Clinical Nursing.* 10(1) pp.94-102.

Garg, A. & Gupta, R. (2014) Predictors of compliance to gluten-free diet in children with celiac disease. *International Scholarly Research Notices.* 2014.

Gasbarrini, G.B., Mangiola, F., Gerardi, V., Ianiro, G., Corazza, G.R. & Gasbarrini, A. (2014) Coeliac disease: An old or a new disease? history of a pathology. *Internal and Emergency Medicine.* 9(3) pp.249-256.

Gee, S.J. & Gibbons, R.A. (1939) *The Coeliac Affection.* Priv. print.

Gehlbach, S.H. (2006) *Interpreting the Medical Literature.* McGraw-Hill, Medical Pub. Division.

Gehlbach, S.H. (1993) *Interpreting the Medical Literature: Stephen H. Gehlbach.* McGraw-Hill, Health Professions Division.

Gerber, B.S., Stolley, M.R., Thompson, A.L., Sharp, L.K. & Fitzgibbon, M.L. (2009) Mobile phone text messaging to promote healthy behaviors and weight loss maintenance: A feasibility study. *Health Informatics Journal.* 15(1) pp.17-25.

Gillies, M. & Baldwin, F. (2001) Do patient information booklets increase perioperative anxiety? *European Journal of Anaesthesiology.* 18(9) pp.620-622.

Giraudet-Le Quintrec, J.S., Coste, J., Vastel, L., Pacault, V., Jeanne, L., Lamas, J.P., Kerboull, L., Fougeray, M., Conseiller, C., Kahan, A. & Courpied, J.P. (2003) Positive effect of patient education for hip surgery: A randomized trial. *Clinical Orthopaedics and Related Research.* (414)(414) pp.112-120.

GKT, H. (2004) Risk of malignancy in diagnosed coeliac disease: A 24-year prospective, population-based, cohort study. *Alimentary Pharmacology & Therapeutics.* 20(7) pp.769-775.

Goh, C. & Banerjee, K. (2007) Prevalence of coeliac disease in children and adolescents with type 1 diabetes mellitus in a clinic based population. *Postgraduate Medical Journal.* 83(976) pp.132-136.

Gold, D.T. & McClung, B. (2006) Approaches to patient education: Emphasizing the long-term value of compliance and persistence. *The American Journal of Medicine.* 119(4) pp.S32-S37.

Goonewardene, M., Shehata, M. & Hamad, A. (2012) Anaemia in pregnancy. *Best Practice & Research Clinical Obstetrics & Gynaecology.* 26(1) pp.3-24.

Goyal, A. & Singh, N. (2007) Consumer perception about fast food in india: An exploratory study. *British Food Journal.* 109(2) pp.182-195.

Gray, A.M. & Papanicolas, I.N. (2010) Impact of symptoms on quality of life before and after diagnosis of coeliac disease: Results from a UK population survey. *BMC Health Services Research.* 10(1) pp.105.

Green, P.H. & Cellier, C. (2007) Celiac disease. *New England Journal of Medicine.* 357(17) pp.1731-1743.

Green, P.H. & Jabri, B. (2003) Coeliac disease. *The Lancet.* 362(9381) pp.383-391.

Green, P.H., Rostami, K. & Marsh, M.N. (2005) Diagnosis of coeliac disease. *Best Practice & Research Clinical Gastroenterology.* 19(3) pp.389-400.

Green, P.H., Stavropoulos, S.N., Panagi, S.G., Goldstein, S.L., McMahon, D.J., Absan, H. & Neugut, A.I. (2001) Characteristics of adult celiac disease in the USA: Results of a national survey. *The American Journal of Gastroenterology.* 96(1) pp.126-131.

Green, P., Alaedini, A., Sander, H., Brannagan, T., Latov, N. & Chin, R. (2005) Mechanisms underlying celiac disease and its neurologic manifestations. *Cellular and Molecular Life Sciences CMLS.* 62(7-8) pp.791-799.

Green, P.H. (2005) The many faces of celiac disease: Clinical presentation of celiac disease in the adult population. *Gastroenterology.* 128(4 Suppl 1) pp.S74-8.

Green, P.H., Fleischauer, A.T., Bhagat, G., Goyal, R., Jabri, B. & Neugut, A.I. (2003) Risk of malignancy in patients with celiac disease. *The American Journal of Medicine.* 115(3) pp.191-195.

Grime, J., Blenkinsopp, A., Raynor, D.K., Pollock, K. & Knapp, P. (2007) The role and value of written information for patients about individual medicines: A systematic review. *Health Expectations.* 10(3) pp.286-298.

Grisolano, S.W., Oxentenko, A.S., Murray, J.A., Burgart, L.J., Dierkhising, R.A. & Alexander, J.A. (2004) The usefulness of routine small bowel biopsies in evaluation of iron deficiency anemia. *Journal of Clinical Gastroenterology.* 38(9) pp.756-760.

Guest, G., Bunce, A. & Johnson, L. (2006a) How many interviews are enough? an experiment with data saturation and variability. *Field Methods.* 18(1) pp.59-82.

Guest, G., Bunce, A. & Johnson, L. (2006b) How many interviews are enough? an experiment with data saturation and variability. *Field Methods.* 18(1) pp.59-82.

Gujral, N., Freeman, H.J. & Thomson, A.B. (2012) Celiac disease: Prevalence, diagnosis, pathogenesis and treatment. *World Journal of Gastroenterology: WJG.* 18(42) pp.6036.

Gülseren, Y.D., Adiloğlu, A.K., Yücel, M., Dağ, Z., Eyerci, N., Berkem, R., Filik, L. & Çaydere, M. (2018) Comparison of non-invasive tests with invasive tests in the diagnosis of celiac disease. *Journal of Clinical Laboratory Analysis.* pp.e22722.

Gupta, R., Reddy, D.N., Makharia, G.K., Sood, A., Ramakrishna, B.S., Yachha, S.K., Thapa, B.R., Banerjee, R., Anuradha, S., Dutta, U., Puri, A.S., Jain, A.K., Mulder, C.J., Kumar, A. & Boindala, S. (2009) Indian task force for celiac disease: Current status. *World Journal of Gastroenterology : WJG.* 15(48) pp.6028-6033.

Haas, K., Martin, A. & Park, K. (2017) Text message intervention (TEACH) improves quality of life and patient activation in celiac disease: A randomized clinical trial. *The Journal of Pediatrics.*

Hadithi, M., von Blomberg, B Mary E, Crusius, J.B.A., Bloemena, E., Kostense, P.J., Meijer, J.W., Mulder, C.J., Stehouwer, C.D. & Pena, A.S. (2007) Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease. *Annals of Internal Medicine.* 147(5) pp.294-302.

Hadjivassiliou, M., Rao, D.G., Wharton, S.B., Sanders, D.S., Grunewald, R.A. & Davies-Jones, A.G. (2010) Sensory ganglionopathy due to gluten sensitivity. *Neurology.* 75(11) pp.1003-1008.

Hære, P., Høie, O., Schulz, T., Schönhardt, I., Raki, M. & Lundin, K.E. (2016) Long-term mucosal recovery and healing in celiac disease is the rule–not the exception. *Scandinavian Journal of Gastroenterology.* 51(12) pp.1439-1446.

Haines, M., Anderson, R. & Gibson, P. (2008) Systematic review: The evidence base for long-term management of coeliac disease. *Alimentary Pharmacology & Therapeutics.* 28(9) pp.1042-1066.

Hall, N.J., Rubin, G.P. & Charnock, A. (2013) Intentional and inadvertent non-adherence in adult coeliac disease. A cross-sectional survey. *Appetite.* 68pp.56-62.

Hall, N.J., Rubin, G. & Charnock, A. (2009) Systematic review: Adherence to a gluten-free diet in adult patients with coeliac disease. *Alimentary Pharmacology & Therapeutics.* 30(4) pp.315-330.

Hallert, C., Grännö, C., Hulten, S., Midhagen, G., Ström, M., Svensson, H. & Valdimarsson, T. (2002) Living with coeliac disease: Controlled study of the burden of illness. *Scandinavian Journal of Gastroenterology.* 37(1) pp.39-42.

Hallert, C., Sandlund, O. & Broqvist, M. (2003) Perceptions of health-related quality of life of men and women living with coeliac disease. *Scandinavian Journal of Caring Sciences.* 17(3) pp.301-307.

Halmos, E.P., Deng, M., Knowles, S.R., Sainsbury, K., Mullan, B. & Tye-Din, J.A. (2018) Food knowledge and psychological state predict adherence to a gluten-free diet in a survey of 5310 australians and new zealanders with coeliac disease. *Alimentary Pharmacology & Therapeutics.* 48(1) pp.78-86.

Halmos, E.P., Di Bella, C.A., Webster, R., Deng, M. & Tye-Din, J.A. (2018) Gluten in “gluten-free” food from food outlets in melbourne: A cross-sectional study. *The Medical Journal of Australia.* 209(1) pp.1.

Hanci, O. & Jeanes, Y. (2018) Cost, availability and nutritional composition comparison between gluten free and gluten containing food staples provided by food outlets and internet food delivery services. In: BSPGHAN Annual Meeting, Wednesday 24th to Friday 26th January 2018. pp.31-31.

Hanna, P. (2012) Using internet technologies (such as skype) as a research medium: A research note. *Qualitative Research.* 12(2) pp.239-242.

Hardy, K., O'brien, S. & Furlong, N. (2001) Information given to patients before appointments and its effect on non-attendance rate. *BMJ: British Medical Journal.* pp.1298-1300.

Harper, J.W., Holleran, S.F., Ramakrishnan, R., Bhagat, G. & Green, P.H. (2007) Anemia in celiac disease is multifactorial in etiology. *American Journal of Hematology.* 82(11) pp.996-1000.

Harris, M. (1986) *Teaching One-to-One: The Writing Conference.* ERIC.

Harvey, C.D. (1988) Telephone survey techniques. *Canadian Home Economics Journal.* 38(1) pp.30-35.

Hauser, W., Gold, J., Stein, J., Caspary, W.F. & Stallmach, A. (2006) Health-related quality of life in adult coeliac disease in germany: Results of a national survey. *European Journal of Gastroenterology & Hepatology.* 18(7) pp.747-754.

Hawkes, N.D., Swift, G.L., Smith, P.M. & Jenkins, H.R. (2000) Incidence and presentation of coeliac disease in south glamorgan. *European Journal of Gastroenterology & Hepatology.* 12(3) pp.345&hyhen.

Heikkilä, K., Heliövaara, M., Impivaara, O., Kröger, H., Knekt, P., Rissanen, H., Mäki, M. & Kaukinen, K. (2015) Celiac disease autoimmunity and hip fracture risk: Findings from a prospective cohort study. *Journal of Bone and Mineral Research.* 30(4) pp.630-636.

Heikkilä, K., Pearce, J., Mäki, M. & Kaukinen, K. (2015) Celiac disease and bone fractures: A systematic review and meta-analysis. *The Journal of Clinical Endocrinology & Metabolism.* 100(1) pp.25-34.

Henry, J.D. & Crawford, J.R. (2005) The short-form version of the depression anxiety stress scales (DASS-21): Construct validity and normative data in a large non-clinical sample. *British Journal of Clinical Psychology.* 44(2) pp.227-239.

Herbert, C.P. (1997) The relevance of cultural diversity to patient education. *Patient Education and Counseling.* 31(2) pp.iii-iv.

Herman, M.L., Rubio–Tapia, A., Lahr, B.D., Larson, J.J., Van Dyke, C.T. & Murray, J.A. (2012) Patients with celiac disease are not followed up adequately. *Clinical Gastroenterology and Hepatology.* 10(8) pp.893-899. e1.

Hietikko, M., Koskinen, O., Kurppa, K., Laurila, K., Saavalainen, P., Salmi, T., Ilus, T., Huhtala, H., Kaukinen, K. & Lindfors, K. (2018) Small-intestinal TG2-specific plasma cells at different stages of coeliac disease. *BMC Immunology.* 19(1) pp.36.

Hill, I.D. (2005) What are the sensitivity and specificity of serologic tests for celiac disease? do sensitivity and specificity vary in different populations? *Gastroenterology.* 128(4) pp.S25-S32.

Hill, A., Roberts, J., Ewings, P. & Gunnell, D. (1997) Non-response bias in a lifestyle survey. *Journal of Public Health Medicine.* 19(2) pp.203-207.

Hofisi, C., Hofisi, M. & Mago, S. (2014) Critiquing interviewing as a data collection method. *Mediterranean Journal of Social Sciences.* 5(16) pp.60.

Högberg, L., Danielsson, L., Jarleman, S., Sundqvist, T. & Stenhammar, L. (2009) Serum zinc in small children with coeliac disease. *Acta Paediatrica.* 98(2) pp.343-345.

Högberg, L., Grodzinsky, E. & Stenhammar, L. (2003) Better dietary compliance in patients with coeliac disease diagnosed in early childhood. *Scandinavian Journal of Gastroenterology.* 38(7) pp.751-754.

Holbrook, A.L., Green, M.C. & Krosnick, J.A. (2003) Telephone versus face-to-face interviewing of national probability samples with long questionnaires: Comparisons of respondent satisficing and social desirability response bias. *Public Opinion Quarterly.* 67(1) pp.79-125.

Holbrook, A.L. & Krosnick, J.A. (2010) Social desirability bias in voter turnout reports tests using the item count technique. *Public Opinion Quarterly.* 74(1) pp.37-67.

Holbrook, A., Krosnick, J.A. & Pfent, A. (2007) The causes and consequences of response rates in surveys by the news media and government contractor survey research firms. *Advances in Telephone Survey Methodology.* pp.499-528.

Hollon, J.R., Cureton, P.A., Martin, M.L., Puppa, E.L.L. & Fasano, A. (2013) Trace gluten contamination may play a role in mucosal and clinical recovery in a subgroup of diet-adherent non-responsive celiac disease patients. *BMC Gastroenterology.* 13(1) pp.40.

Holmboe-Ottesen, G. & Wandel, M. (2012) Changes in dietary habits after migration and consequences for health: A focus on south asians in europe. *Food & Nutrition Research.* 56(1) pp.18891.

Holmes, G.K. & Moor, F. (2012) Coeliac disease in asians in a single centre in southern derbyshire. *Frontline Gastroenterology.* pp.flgastro-2012-100200.

Holmes, G.K. & Muirhead, A. (2017) Epidemiology of coeliac disease in a single centre in southern derbyshire 1958–2014. *BMJ Open Gastroenterology.* 4(1) pp.e000137.

Holmes, G.K., Prior, P., Lane, M.R., Pope, D. & Allan, R.N. (1989) Malignancy in coeliac disease--effect of a gluten free diet. *Gut.* 30(3) pp.333-338.

Holtmeier, W. (2005) Diagnostik der zöliakie/sprue. *Zeitschrift Für Gastroenterologie.* 43(11) pp.1243-1252.

Hopman, E.G., Koopman, H.M., Wit, J.M. & Mearin, M.L. (2009) Dietary compliance and health-related quality of life in patients with coeliac disease. *European Journal of Gastroenterology & Hepatology.* 21(9) pp.1056-1061.

Hopman, E.G., Pruijn, R., Tabben, E.H., le Cessie, S. & Mearin, M.L. (2012) Food questionnaire for the assessment of gluten intake by children 1 to 4 years old. *Journal of Pediatric Gastroenterology and Nutrition.* 54(6) pp.791-796.

Hopper, A., Cross, S. & Sanders, D. (2008) Patchy villous atrophy in adult patients with suspected gluten-sensitive enteropathy: Is a multiple duodenal biopsy strategy appropriate? *Endoscopy.* 40(03) pp.219-224.

Hopper, A.D., Hadjivassiliou, M., Hurlstone, D.P., Lobo, A.J., McAlindon, M.E., Egner, W., Wild, G. & Sanders, D.S. (2008) What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association.* 6(3) pp.314-320.

Houts, P.S., Doak, C.C., Doak, L.G. & Loscalzo, M.J. (2006) The role of pictures in improving health communication: A review of research on attention, comprehension, recall, and adherence. *Patient Education and Counseling.* 61(2) pp.173-190.

Howard, M.R., Turnbull, A.J., Morley, P., Hollier, P., Webb, R. & Clarke, A. (2002) A prospective study of the prevalence of undiagnosed coeliac disease in laboratory defined iron and folate deficiency. *Journal of Clinical Pathology.* 55(10) pp.754-757.

Huang, S., Liu, Y., Zhang, W., Dale, K.J., Liu, S., Zhu, J. & Serventi, L. (2018) Composition of legume soaking water and emulsifying properties in gluten-free bread. *Food Science and Technology International.* 24(3) pp.232-241.

Huang, X. (1994) Patient attitude towards waiting in an outpatient clinic and its applications. *Health Services Management Research.* 7(1) pp.2-8.

Hughey, J.J., Ray, B.K., Lee, A.R., Voorhees, K.N., Kelly, C.P. & Schuppan, D. (2017) Self-reported dietary adherence, disease-specific symptoms, and quality of life are associated with healthcare provider follow-up in celiac disease. *BMC Gastroenterology.* 17(1) pp.156.

Hurley, J.J., Lee, B., Turner, J.K., Beale, A., Jenkins, H.R. & Swift, G.L. (2012) Incidence and presentation of reported coeliac disease in cardiff and the vale of glamorgan: The next 10 years. *European Journal of Gastroenterology & Hepatology.* 24(5) pp.482-486.

Husby, S., Koletzko, S., Korponay-Szabo, I.R., Mearin, M.L., Phillips, A., Shamir, R., Troncone, R., Giersiepen, K., Branski, D., Catassi, C., Lelgeman, M., Maki, M., Ribes-Koninckx, C., Ventura, A., Zimmer, K.P., ESPGHAN Working Group on Coeliac Disease Diagnosis, ESPGHAN Gastroenterology Committee & European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (2012) European society for pediatric gastroenterology, hepatology, and nutrition guidelines for the diagnosis of coeliac disease. *Journal of Pediatric Gastroenterology and Nutrition.* 54(1) pp.136-160.

Hutchinson, J.M., West, N.P., Robins, G.G. & Howdle, P.D. (2010) Long-term histological follow-up of people with coeliac disease in a UK teaching hospital. *QJM : Monthly Journal of the Association of Physicians.* 103(7) pp.511-517.

Iglesias, C. & Torgerson, D. (2000) Does length of questionnaire matter? A randomised trial of response rates to a mailed questionnaire. *Journal of Health Services Research & Policy.* 5(4) pp.219-221.

Ilieva, J., Baron, S. & Healey, N.M. (2002) Online surveys in marketing research: Pros and cons. *International Journal of Market Research.* 44(3) pp.361.

Ivarsson, A., Persson, L., Juto, P., Peltonen, M., Suhr, O. & Hernell, O. (1999) High prevalence of undiagnosed coeliac disease in adults: A swedish population-based study. *Journal of Internal Medicine.* 245(1) pp.63-68.

Ivarsson, A., Persson, L., Nyström, L., Ascher, H., Cavell, B., Danielsson, L., Dannaeus, A., Lindberg, T., Lindquist, B. & Stenhammar, L. (2000) Epidemic of coeliac disease in swedish children. *Acta Paediatrica.* 89(2) pp.165-171.

Ivarsson, A., Persson, L.Å, Nyström, L. & Hernell, O. (2003) The swedish coeliac disease epidemic with a prevailing twofold higher risk in girls compared to boys may reflect gender specific risk factors. *European Journal of Epidemiology.* 18(7) pp.677-684.

Ivarsson, A., Hernell, O., Stenlund, H. & Persson, L.A. (2002) Breast-feeding protects against celiac disease. *The American Journal of Clinical Nutrition.* 75(5) pp.914-921.

Ivarsson, A., Myleus, A., Norstrom, F., van der Pals, M., Rosen, A., Hogberg, L., Danielsson, L., Halvarsson, B., Hammarroth, S., Hernell, O., Karlsson, E., Stenhammar, L., Webb, C., Sandstrom, O. & Carlsson, A. (2013) Prevalence of childhood celiac disease and changes in infant feeding. *Pediatrics.* 131(3) pp.e687-94.

Jaarsma, T., Halfens, R., Huijer Abu-Saad, H., Dracup, K., Gorgels, T., van Ree, J. & Stappers, J. (1999) Effects of education and support on self-care and resource utilization in patients with heart failure. *European Heart Journal.* 20(9) pp.673-682.

Jabri, B. & Sollid, L.M. (2017) T cells in celiac disease. *Journal of Immunology (Baltimore, Md.: 1950).* 198(8) pp.3005-3014.

Jackson, J.L., Chamberlin, J. & Kroenke, K. (2001) Predictors of patient satisfaction. *Social Science & Medicine.* 52(4) pp.609-620.

Jacobsson, L.R., Friedrichsen, M., Goransson, A. & Hallert, C. (2012) Impact of an active patient education program on gastrointestinal symptoms in women with celiac disease following a gluten-free diet: A randomized controlled trial. *Gastroenterology Nursing : The Official Journal of the Society of Gastroenterology Nurses and Associates.* 35(3) pp.200-206.

Jadrešin, O., Mišak, Z., Sanja, K., Sonicki, Z. & Žižic, V. (2008) Compliance with gluten-free diet in children with coeliac disease. *Journal of Pediatric Gastroenterology and Nutrition.* 47(3) pp.344-348.

James, S.P. (2005) National institutes of health consensus development conference statement on celiac disease, june 28–30, 2004. *Gastroenterology.* 128(4) pp.S1-S9.

Janghorban, R., Roudsari, R.L. & Taghipour, A. (2014) Skype interviewing: The new generation of online synchronous interview in qualitative research. *International Journal of Qualitative Studies on Health and Well-Being.* 9.

Jansson-Knodell, C.L., Hujoel, I.A., West, C.P., Taneja, V., Prokop, L.J., Rubio-Tapia, A. & Murray, J.A. (2018) Sex difference in celiac disease in undiagnosed populations–a systematic review and meta-analsysis. *Clinical Gastroenterology and Hepatology.*

Jeanes, Y.M. & Hanci, O. (2018) Are gluten-free food staples accessible to all patients with coeliac disease? *Frontline Gastroenterology.* pp.flgastro-2018-101088.

Jericho, H., Sansotta, N. & Guandalini, S. (2017) Extraintestinal manifestations of celiac disease: Effectiveness of the gluten-free diet. *Journal of Pediatric Gastroenterology and Nutrition.* 65(1) pp.75-79.

Jnawali, P., Kumar, V. & Tanwar, B. (2016) Celiac disease: Overview and considerations for development of gluten-free foods. *Food Science and Human Wellness.* 5(4) pp.169-176.

Joelson, A.M., Geller, M.G., Zylberberg, H.M., Green, P.H. & Lebwohl, B. (2018a) Numbers and features of patients with a diagnosis of celiac disease without duodenal biopsy, based on a national survey. *Clinical Gastroenterology and Hepatology.*

Joelson, A.M., Geller, M.G., Zylberberg, H.M., Green, P.H.R. & Lebwohl, B. (2018b) The effect of depressive symptoms on the association between gluten-free diet adherence and symptoms in celiac disease: Analysis of a patient powered research network. *Nutrients.* 10(5) pp.10.3390/nu10050538.

Johnston, K.L. & White, K.M. (2003) Binge-drinking: A test of the role of group norms in the theory of planned behaviour. *Psychology and Health.* 18(1) pp.63-77.

Johnston, S.D., Rodgers, C. & Watson, R.G. (2004) Quality of life in screen-detected and typical coeliac disease and the effect of excluding dietary gluten. *European Journal of Gastroenterology & Hepatology.* 16(12) pp.1281-1286.

Johnston, S.D., Watson, R.G., McMillan, S.A., Sloan, J. & Love, A.H. (1998) Coeliac disease detected by screening is not silent--simply unrecognized. *QJM : Monthly Journal of the Association of Physicians.* 91(12) pp.853-860.

Kagnoff, M.F. (2005) Overview and pathogenesis of celiac disease. *Gastroenterology.* 128(4) pp.S10-S18.

Kalantar, J.S. & Talley, N.J. (1999) The effects of lottery incentive and length of questionnaire on health survey response rates: A randomized study. *Journal of Clinical Epidemiology.* 52(11) pp.1117-1122.

Kang, J., Kang, A., Green, A., Gwee, K. & Ho, K. (2013) Systematic review: Worldwide variation in the frequency of coeliac disease and changes over time. *Alimentary Pharmacology & Therapeutics.* 38(3) pp.226-245.

Kaplowitz, M.D., Hadlock, T.D. & Levine, R. (2004) A comparison of web and mail survey response rates. *Public Opinion Quarterly.* 68(1) pp.94-101.

Karajeh, M.A., Hurlstone, D.P., Patel, T.M. & Sanders, D.S. (2005) Chefs' knowledge of coeliac disease (compared to the public): A questionnaire survey from the united kingdom. *Clinical Nutrition.* 24(2) pp.206-210.

Karell, K., Louka, A.S., Moodie, S.J., Ascher, H., Clot, F., Greco, L., Ciclitira, P.J., Sollid, L.M., Partanen, J. & European Genetics Cluster on Celiac Disease (2003) HLA types in celiac disease patients not carrying the DQA1* 05-DQB1* 02 (DQ2) heterodimer: Results from the european genetics cluster on celiac disease. *Human Immunology.* 64(4) pp.469-477.

Karnam, U.S., Felder, L.R. & Raskin, J.B. (2004) Prevalence of occult celiac disease in patients with iron-deficiency anemia: A prospective study. *Southern Medical Journal.* 97(1) pp.30-35.

Kasarda, D.D., Okita, T.W., Bernardin, J.E., Baecker, P.A., Nimmo, C.C., Lew, E.J., Dietler, M.D. & Greene, F.C. (1984) Nucleic acid (cDNA) and amino acid sequences of alpha-type gliadins from wheat (triticum aestivum). *Proceedings of the National Academy of Sciences of the United States of America.* 81(15) pp.4712-4716.

Katerina Loucka (2018) Webinar: Are Patient Webinars the Way Forward for NHS. Available at: https://www.digitalhealth.net/events/are-patient-webinars-the-way-forward-for-nhs-futurehealth/ . (Accessed: 19 February 2019).

Katz, S.J., Moyer, C.A., Cox, D.T. & Stern, D.T. (2003) Effect of a triage-based e-mail system on clinic resource use and patient and physician satisfaction in primary care. *Journal of General Internal Medicine.* 18(9) pp.736-744.

Kaukinen, K., Peräaho, M., Lindfors, K., Partanen, J., Woolley, N., Pikkarainen, P., KARVONEN, A., Laasanen, T., Sievänen, H. & Mäki, M. (2007) Persistent small bowel mucosal villous atrophy without symptoms in coeliac disease. *Alimentary Pharmacology & Therapeutics.* 25(10) pp.1237-1245.

Kaukinen, K., Partanen, J., Mäki, M. & Collin, P. (2002a) HLA-DQ typing in the diagnosis of celiac disease. *The American Journal of Gastroenterology.* 97(3) pp.695-699.

Kaukinen, K., Sulkanen, S., Maki, M. & Collin, P. (2002b) IgA-class transglutaminase antibodies in evaluating the efficacy of gluten-free diet in coeliac disease. *European Journal of Gastroenterology & Hepatology.* 14(3) pp.311-315.

Kaur, G., Sarkar, N., Bhatnagar, S., Kumar, S., Rapthap, C., Bhan, M. & Mehra, N. (2002) Pediatric celiac disease in india is associated with multiple DR3-DQ2 haplotypes. *Human Immunology.* 63(8) pp.677-682.

Kavak, U.S., Yüce, A., Koçak, N., Demir, H., Saltik, I.N., Gürakan, F. & Özen, H. (2003) Bone mineral density in children with untreated and treated celiac disease. *Journal of Pediatric Gastroenterology and Nutrition.* 37(4) pp.434-436.

Keeter, S., Kennedy, C., Dimock, M., Best, J. & Craighill, P. (2006) Gauging the impact of growing nonresponse on estimates from a national RDD telephone survey. *Public Opinion Quarterly.* 70(5) pp.759-779.

Kelemen, L.E., Anand, S.S., Vuksan, V., Yi, Q., Teo, K.K., Devanesen, S. & Yusuf, S. (2003) Development and evaluation of cultural food frequency questionnaires for south asians, chinese, and europeans in north america. *Journal of the American Dietetic Association.* 103(9) pp.1178-1184.

Kelle, U. & Bird, K. (1995) *Computer-Aided Qualitative Data Analysis: Theory, Methods and Practice.* Sage.

Kemppainen, T., Kröger, H., Janatuinen, E., Arnala, I., Kosma, V., Pikkarainen, P., Julkunen, R., Jurvelin, J., Alhava, E. & Uusitupa, M. (1999a) Osteoporosis in adult patients with celiac disease. *Bone.* 24(3) pp.249-255.

Kemppainen, T., Kroger, H., Janatuinen, E., Arnala, I., Lamberg-Allardt, C., Karkkainen, M., Kosma, V.M., Julkunen, R., Jurvelin, J., Alhava, E. & Uusitupa, M. (1999b) Bone recovery after a gluten-free diet: A 5-year follow-up study. *Bone.* 25(3) pp.355-360.

Kenrick, K. & Day, A.S. (2014) Coeliac disease: Where are we in 2014? *Australian Family Physician.* 43(10) pp.674.

Kenwright, M., Marks, I., Graham, C., Franses, A. & Mataix-Cols, D. (2005) Brief scheduled phone support from a clinician to enhance computer-aided self-help for obsessive-compulsive disorder: Randomized controlled trial. *Journal of Clinical Psychology.* 61(12) pp.1499-1508.

Khemiri, M., Ouederni, M., Khaldi, F. & Barsaoui, S. (2008) Screening for celiac disease in idiopathic pulmonary hemosiderosis. *Gastroenterologie Clinique Et Biologique.* 32(8-9) pp.745-748.

Khoshoo, V. & Bhan, M.K. (1989) Celiac disease in indian children. *Indian Pediatrics.* 26(7) pp.627-629.

Khurana, B., Lomash, A., Khalil, S., Bhattacharya, M., Rajeshwari, K. & Kapoor, S. (2015) Evaluation of the impact of celiac disease and its dietary manipulation on children and their caregivers. *Indian Journal of Gastroenterology.* 34(2) pp.112-116.

King, N., Cassell, C. & Symon, G. (2004) Using templates in the thematic analysis of text. *Essential Guide to Qualitative Methods in Organizational Research.* 2pp.256-270.

Kinsey, L., Burden, S. & Bannerman, E. (2007) A dietary survey to determine if patients with coeliac disease are meeting current healthy eating guidelines and how their diet compares to that of the british general population. *European Journal of Clinical Nutrition.* 62(11) pp.1333-1342.

Kirchner, C. & Schmeidler, E. (2001) Adding audio description: Does it make a difference? *Journal of Visual Impairment & Blindness (JVIB).* 95(04) .

Kochhar, R., Jain, K., Thapa, B.R., Rawal, P., Khaliq, A., Kochhar, R., Bhadada, S., Vaiphei, K., Varma, S. & Dutta, U. (2012) Clinical presentation of celiac disease among pediatric compared to adolescent and adult patients. *Indian Journal of Gastroenterology.* 31(3) pp.116-120.

Kochhar, R., Sachdev, S., Kochhar, R., Aggarwal, A., Sharma, V., Prasad, K.K., Singh, G., Nain, C.K., Singh, K. & Marwaha, N. (2012) Prevalence of coeliac disease in healthy blood donors: A study from north india. *Digestive and Liver Disease.* 44(6) pp.530-532.

Kochhar, G.S., Singh, T., Gill, A. & Kirby, D.F. (2016) Celiac disease: Managing a multisystem disorder. *Cleveland Clinic Journal of Medicine.* 83(3) pp.217-227.

Kocsis, D., Miheller, P., Lőrinczy, K., Herszényi, L., Tulassay, Z., Rácz, K. & Juhász, M. (2013) Coeliac disease in a 15-year period of observation (1997 and 2011) in a hungarian referral centre. *European Journal of Internal Medicine.* 24(5) pp.461-467.

Kolho, K., Färkkilä, M. & Savilahti, E. (1998) Undiagnosed coeliac disease is common in finnish adults. *Scandinavian Journal of Gastroenterology.* 33(12) pp.1280-1283.

Korponay-Szabo, I.R., Dahlbom, I., Laurila, K., Koskinen, S., Woolley, N., Partanen, J., Kovacs, J.B., Maki, M. & Hansson, T. (2003) Elevation of IgG antibodies against tissue transglutaminase as a diagnostic tool for coeliac disease in selective IgA deficiency. *Gut.* 52(11) pp.1567-1571.

Kothe, E.J., Sainsbury, K., Smith, L. & Mullan, B.A. (2015) Explaining the intention–behaviour gap in gluten-free diet adherence: The moderating roles of habit and perceived behavioural control. *Journal of Health Psychology.* 20(5) pp.580-591.

Kotze, L.M. (2004) Gynecologic and obstetric findings related to nutritional status and adherence to a gluten-free diet in brazilian patients with celiac disease. *Journal of Clinical Gastroenterology.* 38(7) pp.567-574.

Kreuter, F., Presser, S. & Tourangeau, R. (2008) Social desirability bias in CATI, IVR, and web SurveysThe effects of mode and question sensitivity. *Public Opinion Quarterly.* 72(5) pp.847-865.

Krumholz, H.M., Amatruda, J., Smith, G.L., Mattera, J.A., Roumanis, S.A., Radford, M.J., Crombie, P. & Vaccarino, V. (2002) Randomized trial of an education and support intervention to preventreadmission of patients with heart failure. *Journal of the American College of Cardiology.* 39(1) pp.83-89.

Krupa-Kozak, U. (2014) Pathologic bone alterations in celiac disease: Etiology, epidemiology, and treatment. *Nutrition (Burbank, Los Angeles County, Calif.).* 30(1) pp.16-24.

Kuja-Halkola, R., Lebwohl, B., Halfvarson, J., Emilsson, L., Magnusson, P.K. & Ludvigsson, J.F. (2017) Birth weight, sex, and celiac disease: A nationwide twin study. *Clinical Epidemiology.* 9pp.567.

Kumar, D.M., Symonds, R.P., Sundar, S., Ibrahim, K., Savelyich, B. & Miller, E. (2004) Information needs of asian and white british cancer patients and their families in leicestershire: A cross-sectional survey. *British Journal of Cancer.* 90(8) pp.1474-1478.

Kumar, S. & Phrommathed, P. (2005) *Research Methodology.* Springer.

Kumar, N., Gross, J.B.,Jr & Ahlskog, J.E. (2004) Copper deficiency myelopathy produces a clinical picture like subacute combined degeneration. *Neurology.* 63(1) pp.33-39.

Kumarasamy, N., Safren, S.A., Raminani, S.R., Pickard, R., James, R., Krishnan, A.S., Solomon, S. & Mayer, K.H. (2005) Barriers and facilitators to antiretroviral medication adherence among patients with HIV in chennai, india: A qualitative study. *AIDS Patient Care & STDs.* 19(8) pp.526-537.

Kurien, M., Trott, N. & Sanders, D.S. (2016) Long-term care for patients with coeliac disease in the UK: A review of the literature and future directions. *Journal of Human Nutrition and Dietetics.* 29(5) pp.617-623.

Kurppa, K., Collin, P., Viljamaa, M., Haimila, K., Saavalainen, P., Partanen, J., Laurila, K., Huhtala, H., Paasikivi, K., Maki, M. & Kaukinen, K. (2009) Diagnosing mild enteropathy celiac disease: A randomized, controlled clinical study. *Gastroenterology.* 136(3) pp.816-823.

Kurppa, K., Paavola, A., Collin, P., Sievanen, H., Laurila, K., Huhtala, H., Saavalainen, P., Maki, M. & Kaukinen, K. (2014) Benefits of a gluten-free diet for asymptomatic patients with serologic markers of celiac disease. *Gastroenterology.*

Laass, M.W., Röber, N., Range, U., Noß, L., Roggenbuck, D. & Conrad, K. (2015) Loss and gain of tolerance to pancreatic glycoprotein 2 in celiac disease. *PLoS One.* 10(6) pp.e0128104.

Lähdeaho, M., Mäki, M., Laurila, K., Huhtala, H. & Kaukinen, K. (2011) Small-bowel mucosal changes and antibody responses after low-and moderate-dose gluten challenge in celiac disease. *BMC Gastroenterology.* 11(1) pp.129.

Lamontagne, P., West, G.E. & Galibois, I. (2001) Quebecers with celiac disease: Analysis of dietary problems. *Canadian Journal of Dietetic Practice and Research.* 62(4) pp.175.

Lanzini, A., Lanzarotto, F., Villanacci, V., Mora, A., Bertolazzi, S., Turini, D., Carella, G., Malagoli, A., Ferrante, G. & Cesana, B. (2009) Complete recovery of intestinal mucosa occurs very rarely in adult coeliac patients despite adherence to gluten-free diet. *Alimentary Pharmacology & Therapeutics.* 29(12) pp.1299-1308.

Lara, L.F., Cisneros, G., Gurney, M., Van Ness, M., Jarjoura, D., Moauro, B., Polen, A., Rutecki, G. & Whittier, F. (2003) One-day quadruple therapy compared with 7-day triple therapy for helicobacter pylori infection. *Archives of Internal Medicine.* 163(17) pp.2079-2084.

Larussa, T., Suraci, E., Imeneo, M., Marasco, R. & Luzza, F. (2017) Normal bone mineral density associates with duodenal mucosa healing in adult patients with celiac disease on a gluten-free diet. *Nutrients.* 9(2) pp.98.

Laszkowska, M., Mahadev, S., Sundström, J., Lebwohl, B., Green, P., Michaelsson, K. & Ludvigsson, J.F. (2018) Systematic review with meta-analysis: The prevalence of coeliac disease in patients with osteoporosis. *Alimentary Pharmacology & Therapeutics.* 48(6) pp.590-597.

Lau, M.S., Mooney, P.D., Rees, M.A., White, W.L., Marks, L.J., Hadjivassiliou, M. & Sanders, D.S. (2018) *OWE-022 Gluten Free Diet Adherence Assessment using CDAT and BIAGI Questionnaires in Patients with Coeliac Disease.*

Laurikka, P., Salmi, T., Collin, P., Huhtala, H., Mäki, M., Kaukinen, K. & Kurppa, K. (2016) Gastrointestinal symptoms in celiac disease patients on a long-term gluten-free diet. *Nutrients.* 8(7) pp.429.

Lawton, J., Ahmad, N., Hanna, L., Douglas, M., Bains, H. & Hallowell, N. (2008) 'We should change ourselves, but we can't': Accounts of food and eating practices amongst british pakistanis and indians with type 2 diabetes. *Ethnicity & Health.* 13(4) pp.305-319.

Lea, M.E., Harbord, M. & Sage, M.R. (1995) Bilateral occipital calcification associated with celiac disease, folate deficiency, and epilepsy. *AJNR.American Journal of Neuroradiology.* 16(7) pp.1498-1500.

Lebwohl, B., Murray, J.A., Rubio-Tapia, A., Green, P.H. & Ludvigsson, J.F. (2014a) Predictors of persistent villous atrophy in coeliac disease: A population-based study. *Alimentary Pharmacology & Therapeutics.* 39(5) pp.488-495.

Lebwohl, B., Eriksson, H., Hansson, J., Green, P.H. & Ludvigsson, J.F. (2014b) Risk of cutaneous malignant melanoma in patients with celiac disease: A population-based study. *Journal of the American Academy of Dermatology.*

Lee, A., Ng, D., Zivin, J. & Green, P. (2007a) Economic burden of a gluten-free diet. *Journal of Human Nutrition and Dietetics.* 20(5) pp.423-430.

Lee, H.J., Anderson, Z. & Ryu, D. (2014) Gluten contamination in foods labeled as "Gluten free" in the united states. *Journal of Food Protection®.* 77(10) pp.1830-1833.

Lee, S.K., Lo, W., Memeo, L., Rotterdam, H. & Green, P.H. (2003) Duodenal histology in patients with celiac disease after treatment with a gluten-free diet. *Gastrointestinal Endoscopy.* 57(2) pp.187-191.

Lee, Y. & Lin, J.L. (2010) Do patient autonomy preferences matter? linking patient-centered care to patient–physician relationships and health outcomes. *Social Science & Medicine.* 71(10) pp.1811-1818.

Lee, J. & Clarke, K. (2017) Effect of clinical and laboratory parameters on quality of life in celiac patients using celiac disease-specific quality of life scores. *Scandinavian Journal of Gastroenterology.* 52(11) pp.1235-1239.

Leeds, J., Hopper, A., Hurlstone, D., Edwards, S., McAlindon, M., Lobo, A., Donnelly, M., Morley, S. & Sanders, D. (2007) Is exocrine pancreatic insufficiency in adult coeliac disease a cause of persisting symptoms? *Alimentary Pharmacology & Therapeutics.* 25(3) pp.265-271.

Leffler, D.A., Dennis, M., Edwards George, J.B., Jamma, S., Magge, S., Cook, E.F., Schuppan, D. & Kelly, C.P. (2009) A simple validated gluten-free diet adherence survey for adults with celiac disease. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association.* 7(5) pp.530-6, 536.e1-2.

Leffler, D.A., Edwards George, J.B., Dennis, M., Cook, E.F., Schuppan, D. & Kelly, C.P. (2007) A prospective comparative study of five measures of gluten-free diet adherence in adults with coeliac disease. *Alimentary Pharmacology & Therapeutics.* 26(9) pp.1227-1235.

Leffler, D.A., Edwards-George, J., Dennis, M., Schuppan, D., Cook, F., Franko, D.L., Blom-Hoffman, J. & Kelly, C.P. (2008) Factors that influence adherence to a gluten-free diet in adults with celiac disease. *Digestive Diseases and Sciences.* 53(6) pp.1573-1581.

Legard, R., Keegan, J. & Ward, K. (2003) In-depth interviews. *Qualitative Research Practice: A Guide for Social Science Students and Researchers.* pp.138-169.

Leicester City Council (2018) *Setting the Context – Leicester's Demographic Profile*. Available at: https://www.leicester.gov.uk/media/183446/cyp-jsna-chapter-one-setting-the-context.pdf . (Accessed: 19 February 2019)

Levin, K.A. (2006) Study design III: Cross-sectional studies. *Evidence-Based Dentistry.* 7(1) pp.24-25.

Levran, N., Wilschanski, M., Livovsky, J., Shachar, E., Moskovitz, M., Assaf-Jabrin, L. & Shteyer, E. (2018) Obesogenic habits among children and their families in response to initiation of gluten-free diet. *European Journal of Pediatrics.* 177(6) pp.859-866.

Lewis, H., Renaula, T., Garioch, J., Leonard, J., Fry, J., Collin, P., Evans, D. & Fry, L. (1996) Protective effect of gluten-free diet against development of lymphoma in dermatitis herpetiformis. *British Journal of Dermatology.* 135(3) pp.363-367.

Lietz, P. (2010) Research into questionnaire design. *International Journal of Market Research.* 52(2) pp.249-272.

Likert, R. (1932) A technique for the measurement of attitudes. *Archives of Psychology.*

Lim Fat, M.J., Doja, A., Barrowman, N. & Sell, E. (2011) YouTube videos as a teaching tool and patient resource for infantile spasms. *Journal of Child Neurology.* 26(7) pp.804-809.

Lind, M.V., Madsen, M.L., Rumessen, J.J., Vestergaard, H., Gøbel, R.J., Hansen, T., Lauritzen, L., Pedersen, O.B., Kristensen, M. & Ross, A.B. (2016) Plasma alkylresorcinol concentrations as a novel measure of compliance to a gluten-free diet. *The FASEB Journal.* 30(1_supplement) pp.lb266-lb266.

Lindfors, K., Mäki, M. & Kaukinen, K. (2010) Transglutaminase 2-targeted autoantibodies in celiac disease: Pathogenetic players in addition to diagnostic tools? *Autoimmunity Reviews.* 9(11) pp.744-749.

Lionel, F. (2002) Dermatitis herpetiformis: Problems, progress and prospects. *European Journal of Dermatology.* 12(6) pp.523-531.

Lionetti, E., Castellaneta, S., Francavilla, R., Pulvirenti, A., Catassi, C., of Weaning, SIGENP Working Group & Risk, C. (2017) Mode of delivery and risk of celiac disease: Risk of celiac disease and age at gluten introduction cohort study. *The Journal of Pediatrics.* 184pp.81-86. e2.

Lionetti, E., Castellaneta, S., Pulvirenti, A., Tonutti, E., Francavilla, R., Fasano, A., Catassi, C., of Weaning, Italian Working Group & Risk, C.D. (2012) Prevalence and natural history of potential celiac disease in at-family-risk infants prospectively investigated from birth. *The Journal of Pediatrics.* 161(5) pp.908-914. e2.

Lohi, S., Mustalahti, K., Kaukinen, K., Laurila, K., Collin, P., Rissanen, H., Lohi, O., Bravi, E., Gasparin, M., Reunanen, A. & Maki, M. (2007) Increasing prevalence of coeliac disease over time. *Alimentary Pharmacology & Therapeutics.* 26(9) pp.1217-1225.

Losowsky, M.S. (2008) A history of coeliac disease. *Digestive Diseases (Basel, Switzerland).* 26(2) pp.112-120.

Lovibond, S. & Lovibond, P. (1995) Manual for the depression anxiety stress scales. 2nd edn. sydney: Psychology foundation, 1995. In: Lovibond, S. (ed.) *Google Scholar.* pp.4-42.

Ludvigsson, J.F., Montgomery, S.M. & Ekbom, A. (2007) Risk of pancreatitis in 14,000 individuals with celiac disease. *Clinical Gastroenterology and Hepatology.* 5(11) pp.1347-1353. e2.

Ludvigsson, J.F., Montgomery, S.M., Ekbom, A., Brandt, L. & Granath, F. (2009) Small-intestinal histopathology and mortality risk in celiac disease. *Jama.* 302(11) pp.1171-1178.

Ludvigsson, J.F., Neovius, M. & Hammarström, L. (2014a) Association between IgA deficiency & other autoimmune conditions: A population-based matched cohort study. *Journal of Clinical Immunology.* 34(4) pp.444-451.

Ludvigsson, J.F., Rubio-Tapia, A., Van Dyke, C.T., Melton, L.J., Zinsmeister, A.R., Lahr, B.D. & Murray, J.A. (2013a) Increasing incidence of celiac disease in a north american population. *The American Journal of Gastroenterology.* 108(5) pp.818-824.

Ludvigsson, J.F., Bai, J.C., Biagi, F., Card, T.R., Ciacci, C., Ciclitira, P.J., Green, P.H., Hadjivassiliou, M., Holdoway, A., van Heel, D.A., Kaukinen, K., Leffler, D.A., Leonard, J.N., Lundin, K.E., McGough, N., Davidson, M., Murray, J.A., Swift, G.L., Walker, M.M., Zingone, F., Sanders, D.S. & Authors of the BSG Coeliac Disease Guidelines Development Group (2014b) Diagnosis and management of adult coeliac disease: Guidelines from the british society of gastroenterology. *Gut.* 63(8) pp.1210-1228.

Ludvigsson, J.F., Leffler, D.A., Bai, J.C., Biagi, F., Fasano, A., Green, P.H., Hadjivassiliou, M., Kaukinen, K., Kelly, C.P., Leonard, J.N., Lundin, K.E., Murray, J.A., Sanders, D.S., Walker, M.M., Zingone, F. & Ciacci, C. (2013b) The oslo definitions for coeliac disease and related terms. *Gut.* 62(1) pp.43-52.

Lyratzopoulos, G., Elliott, M., Barbiere, J.M., Henderson, A., Staetsky, L., Paddison, C., Campbell, J. & Roland, M. (2012) Understanding ethnic and other socio-demographic differences in patient experience of primary care: Evidence from the english general practice patient survey. *BMJ Quality & Safety.* 21(1) pp.21-29.

MacCulloch, K. & Rashid, M. (2014) Factors affecting adherence to a gluten-free diet in children with celiac disease. *Paediatrics & Child Health.* 19(6) pp.305-309.

Mager, D.R., Marcon, M., Brill, H., Liu, A., Radmanovich, K., Mileski, H., Nasser, R., Alzaben, A., Carroll, M.W., Yap, J., Persad, R. & Turner, J.M. (2018) Adherence to the gluten-free diet and health-related quality of life in an ethnically diverse pediatric population with celiac disease. *Journal of Pediatric Gastroenterology and Nutrition.* 66(6) pp.941-948.

Mahadev, S., Simpson, S., Lebwohl, B., Lewis, S.K., Tennyson, C.A. & Green, P.H. (2013) Is dietitian use associated with celiac disease outcomes? *Nutrients.* 5(5) pp.1585-1594.

Mahadev, S., Laszkowska, M., Sundstrom, J., Bjorkholm, M., Lebwohl, B., Green, P.H.R. & Ludvigsson, J.F. (2018) Prevalence of celiac disease in patients with iron deficiency anemia-A systematic review with meta-analysis. *Gastroenterology.* 155(2) pp.374-382.e1.

Maiuri, L., Ciacci, C., Ricciardelli, I., Vacca, L., Raia, V., Auricchio, S., Picard, J., Osman, M., Quaratino, S. & Londei, M. (2003) Association between innate response to gliadin and activation of pathogenic T cells in coeliac disease. *The Lancet.* 362(9377) pp.30-37.

Maiwall, R., Goel, A., Pulimood, A.B., Babji, S., Sophia, J., Prasad, C., Balasubramanian, K., Ramakrishna, B., Kurian, S. & Fletcher, G.J. (2014) Investigation into celiac disease in indian patients with portal hypertension. *Indian Journal of Gastroenterology.* pp.1-7.

Makharia, G.K., Verma, A.K., Amarchand, R., Bhatnagar, S., Das, P., Goswami, A., Bhatia, V., Ahuja, V., Datta Gupta, S. & Anand, K. (2011) Prevalence of celiac disease in the northern part of india: A community based study. *Journal of Gastroenterology and Hepatology.* 26(5) pp.894-900.

Mäki, M. (2012) Coeliac disease: Lack of consensus regarding definitions of coeliac disease. *Nature Reviews Gastroenterology and Hepatology.* 9(6) pp.305.

Maki, M., Mustalahti, K., Kokkonen, J., Kulmala, P., Haapalahti, M., Karttunen, T., Ilonen, J., Laurila, K., Dahlbom, I., Hansson, T., Hopfl, P. & Knip, M. (2003) Prevalence of celiac disease among children in finland. *The New England Journal of Medicine.* 348(25) pp.2517-2524.

Malamut, G. (2012) La maladie cœliaque. *Médecine & Nutrition.* 48(4) pp.24-27.

Malamut, G., Murray, J.A. & Cellier, C. (2012) Refractory celiac disease. *Gastrointestinal Endoscopy Clinics of North America.* 22(4) pp.759-772.

Malavige, L.S., Wijesekara, P., Epa, D.S., Ranasinghe, P. & Levy, J.C. (2015) Ethnicity and neighbourhood deprivation determines the response rate in sexual dysfunction surveys. *BMC Research Notes.* 8(1) pp.410.

Malekzadeh, R., Sachdev, A. & Fahid Ali, A. (2005) Coeliac disease in developing countries: Middle east, india and north africa. *Best Practice & Research.Clinical Gastroenterology.* 19(3) pp.351-358.

Mannino, M., Cellura, E., Grimaldi, G., Volanti, P., Piccoli, F. & La Bella, V. (2007) Telephone follow-up for patients with amyotrophic lateral sclerosis. *European Journal of Neurology.* 14(1) pp.79-84.

Mansikka, E., Hervonen, K., Kaukinen, K., Collin, P., Huhtala, H., Reunala, T. & Salmi, T. (2018) Prognosis of dermatitis herpetiformis patients with and without villous atrophy at diagnosis. *Nutrients.* 10(5) pp.641.

Mansoor, L.E. & Dowse, R. (2003) Effect of pictograms on readability of patient information materials. *The Annals of Pharmacotherapy.* 37(7-8) pp.1003-1009.

Mant, M.J., Bain, V.G., Maguire, C.G., Murland, K. & Yacyshyn, B.R. (2006) Prevalence of occult gastrointestinal bleeding in celiac disease. *Clinical Gastroenterology and Hepatology.* 4(4) pp.451-454.

Marcus, A.C. & Crane, L.A. (1986) Telephone surveys in public health research. *Medical Care.* pp.97-112.

Marklund, B., Ström, M., Månsson, J., Borgquist, L., Baigi, A. & Fridlund, B. (2007) Computer-supported telephone nurse triage: An evaluation of medical quality and costs. *Journal of Nursing Management.* 15(2) pp.180-187.

Marsh, M.N. & Crowe, P.T. (1995) 5 morphology of the mucosal lesion in gluten sensitivity. *Baillière's Clinical Gastroenterology.* 9(2) pp.273-293.

Marsh, M.N. (2013) Defining 'coeliac': Oslo accord--or not? *Gut.* 62(11) pp.1669-1670.

Marsh, M.N. (1990) Grains of truth: Evolutionary changes in small intestinal mucosa in response to environmental antigen challenge. *Gut.* 31(1) pp.111-114.

Marshall, B., Cardon, P., Poddar, A. & Fontenot, R. (2013) Does sample size matter in qualitative research?: A review of qualitative interviews in IS research. *Journal of Computer Information Systems.* 54(1) pp.11-22.

Marshall, M.N. (1996) Sampling for qualitative research. *Family Practice.* 13(6) pp.522-526.

Martin, P.Y. & Turner, B.A. (1986) Grounded theory and organizational research. *The Journal of Applied Behavioral Science.* 22(2) pp.141-157.

Martin, U. & Mercer, S. (2014) A comparison of general practitioners prescribing of gluten-free foods for the treatment of coeliac disease with national prescribing guidelines. *Journal of Human Nutrition and Dietetics.* 27(1) pp.96-104.

Masood, N. & Ali Shaikh, I. (2014) Clinical presentations and biochemical profile in adult celiac disease patients in hyderabad: Pakistan. *Pakistan Journal of Medical Sciences.* 30(2) pp.287-290.

Max, J.E., 2017. Jack Fell Down and Broke His Crown: Not Unusual and So Why the Skype?. *Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(11), pp.916-917. doi: 10.1016/j.jaac.2017.09.416

Maxwell, J.A., 2012. *Qualitative research design: An interactive approach* (Vol. 41). Sage publications Los-Angeles, Chapter 3, pp.41-71

Mazor, K.M., Clauser, B.E., Field, T., Yood, R.A. & Gurwitz, J.H. (2002) A demonstration of the impact of response bias on the results of patient satisfaction surveys. *Health Services Research.* 37(5) pp.1403-1417.

McAllister, B.P., Williams, E. & Clarke, K. (2018) A comprehensive review of celiac disease/gluten-sensitive enteropathies. *Clinical Reviews in Allergy & Immunology.* pp.1-18.

McCarney, R., Warner, J., Iliffe, S., Van Haselen, R., Griffin, M. & Fisher, P. (2007) The hawthorne effect: A randomised, controlled trial. *BMC Medical Research Methodology.* 7(1) pp.30.

McCarthy, K., McGee, H. & O'Boyle, C. (2000) Outpatient clinic waiting times and non-attendance as indicators of quality. *Psychology, Health & Medicine.* 5(3) pp.287-293.

McCarty, T.R., O'Brien, C.R., Gremida, A., Ling, C. & Rustagi, T. (2018) Efficacy of duodenal bulb biopsy for diagnosis of celiac disease: A systematic review and meta-analysis. *Endoscopy International Open.* 6(11) pp.E1369-E1378.

McClure, R.J., Newell, S.J. & Edwards, S. (1996) Patient characteristics affecting attendance at general outpatient clinics. *Archives of Disease in Childhood.* 74(2) pp.121-125.

McDade, T.W., Williams, S. & Snodgrass, J.J. (2007) What a drop can do: Dried blood spots as a minimally invasive method for integrating biomarkers into population-based research. *Demography.* 44(4) pp.899-925.

McFarlane, X.A., Bhalla, A.K., Reeves, D.E., Morgan, L.M. & Robertson, D.A. (1995) Osteoporosis in treated adult coeliac disease. *Gut.* 36(5) pp.710-714.

McGough, N. & Cummings, J.H. (2005) Coeliac disease: A diverse clinical syndrome caused by intolerance of wheat, barley and rye. *Proceedings of the Nutrition Society.* 64(4) pp.434-450.

McGowan, K.E., Lyon, M.E. & Butzner, J.D. (2008) Celiac disease and IgA deficiency: Complications of serological testing approaches encountered in the clinic. *Clinical Chemistry.* 54(7) pp.1203-1209.

McHorney, C.A., Kosinski, M. & Ware Jr, J.E. (1994) Comparisons of the costs and quality of norms for the SF-36 health survey collected by mail versus telephone interview: Results from a national survey. *Medical Care.* pp.551-567.

McIntosh, J., Flanagan, A., Madden, N., Mulcahy, M., Dargan, L., Walker, M. & Burns, D.T. (2011) Awareness of coeliac disease and the gluten status of 'gluten-free'food obtained on request in catering outlets in ireland. *International Journal of Food Science & Technology.* 46(8) pp.1569-1574.

Mealer, M. & Jones, J. (2014) Methodological and ethical issues related to qualitative telephone interviews on sensitive topics. *Nurse Researcher.* 21(4) .

Mealing, N.M., Banks, E., Jorm, L.R., Steel, D.G., Clements, M.S. & Rogers, K.D. (2010) Investigation of relative risk estimates from studies of the same population with contrasting response rates and designs. *BMC Medical Research Methodology.* 10(1) pp.26.

Mearns, E.S., Taylor, A., Boulanger, T., Craig, K.J., Gerber, M., Leffler, D.A., Drahos, J., Sanders, D.S. & Lebwohl, B. (2018) Systematic literature review of the economic burden of celiac disease. *PharmacoEconomics.* pp.1-17.

Meeuwisse, G. (1970) Round table discussion. *Diagnostic Criteria In.*

Megiorni, F., Mora, B., Bonamico, M., Barbato, M., Montuori, M., Viola, F., Trabace, S. & Mazzilli, M.C. (2008) HLA-DQ and susceptibility to celiac disease: Evidence for gender differences and parent-of-origin effects. *The American Journal of Gastroenterology.* 103(4) pp.997-1003.

Megiorni, F. & Pizzuti, A. (2012) HLA-DQA1 and HLA-DQB1 in celiac disease predisposition: Practical implications of the HLA molecular typing. *Journal of Biomedical Science.* 19(1) pp.88.

Mehta, P., Pan, Z., Riley, M.D. & Liu, E. (2018) Adherence to a gluten-free diet: Assessment by dietitian interview and serology. *Journal of Pediatric Gastroenterology and Nutrition.* 66(3) pp.e67-e70.

Meilleur, K.G. & Littleton-Kearney, M.T. (2009) Interventions to improve patient education regarding multifactorial genetic conditions: A systematic review. *American Journal of Medical Genetics Part A.* 149(4) pp.819-830.

Mention, J., Ben Ahmed, M., Bègue, B., Barbe, U., Verkarre, V., Asnafi, V., Colombel, J., Cugnenc, P., Ruemmele, F.M. & Mcintyre, E. (2003) Interleukin 15: A key to disrupted intraepithelial lymphocyte homeostasis and lymphomagenesis in celiac disease. *Gastroenterology.* 125(3) pp.730-745.

Metso, S., Hyytiä-Ilmonen, H., Kaukinen, K., Huhtala, H., Jaatinen, P., Salmi, J., Taurio, J. & Collin, P. (2012) Gluten-free diet and autoimmune thyroiditis in patients with celiac disease. A prospective controlled study. *Scandinavian Journal of Gastroenterology.* 47(1) pp.43-48.

Metz, J.A., Kris-Etherton, P.M., Morris, C.D., Mustad, V.A., Stern, J.S., Oparil, S., Chait, A., Haynes, R.B., Resnick, L.M., Clark, S., Hatton, D.C., McMahon, M., Holcomb, S., Snyder, G.W., Pi-Sunyer, F.X. & McCarron, D.A. (1997) Dietary compliance and cardiovascular risk reduction with a prepared meal plan compared with a self-selected diet. *The American Journal of Clinical Nutrition.* 66(2) pp.373-385.

Meyer, D., Stavropolous, S., Diamond, B., Shane, E. & Green, P.H. (2001) Osteoporosis in a north american adult population with celiac disease. *The American Journal of Gastroenterology.* 96(1) pp.112-119.

Meyer, K.G., Fasshauer, M., Nebel, I.T. & Paschke, R. (2004) Comparative analysis of conventional training and a computer-based interactive training program for celiac disease patients. *Patient Education and Counseling.* 54(3) pp.353-360.

Meyer, S. & Rosenblum, S. (2018) Daily experiences and challenges among children and adolescents with celiac disease: Focus group results. *Journal of Pediatric Gastroenterology and Nutrition.* 66(1) pp.58-63.

Michie, S., van Stralen, M.M. & West, R. (2011) The behaviour change wheel: A new method for characterising and designing behaviour change interventions. *Implementation Science.* 6(1) pp.42.

Miller, L.L. & Aharoni, E. (2015) *Understanding Low Survey Response Rates among Young US Military Personnel.*

Millington, R.S., James-Galton, M., Barbur, J.L., Plant, G.T. & Bridge, H. (2015) Severe, persistent visual impairment associated with occipital calcification and coeliac disease. *Journal of Neurology.* 262(9) pp.2056-2063.

Mintel's global public relations team (2015) ***Half of Americans Think Gluten-Free Diets are a Fad while 25% Eat Gluten-Free Foods***. Available at: http://www.mintel.com/press-centre/food-and-drink/half-of-americans-think-gluten-free-diets-are-a-fad-while-25-eat-gluten-free-foods . (Accessed: 19 February 2019).

Mitea, C., Havenaar, R., Drijfhout, J.W., Edens, L., Dekking, L. & Koning, F. (2008) Efficient degradation of gluten by a prolyl endoprotease in a gastrointestinal model: Implications for coeliac disease. *Gut.* 57(1) pp.25-32.

Mohr, D.C., Vella, L., Hart, S., Heckman, T. & Simon, G. (2008) The effect of telephone-administered psychotherapy on symptoms of depression and attrition: A meta-analysis. *Clinical Psychology: Science and Practice.* 15(3) pp.243-253.

Molberg, Ø, Mcadam, S.N., Korner, R., Quarsten, H., Kristiansen, C., Madsen, L., Fugger, L., Scott, H., Noren, O. & Roepstorff, P. (1998) Tissue transglutaminase selectively modifies gliadin peptides that are recognized by gut-derived T cells in celiac disease. *Nature Medicine.* 4(6) pp.713-717.

Monaghan, J., Channell, K., McDowell, D. & Sharma, A.K. (2005) Improving patient and carer communication, multidisciplinary team working and goal-setting in stroke rehabilitation. *Clinical Rehabilitation.* 19(2) pp.194-199.

Monzani, A., Rapa, A., Fonio, P., Tognato, E., Panigati, L. & Oderda, G. (2011) Use of deamidated gliadin peptide antibodies to monitor diet compliance in childhood celiac disease. *Journal of Pediatric Gastroenterology and Nutrition.* 53(1) pp.55-60.

Mora, S., Barera, G., Beccio, S., Proverbio, M.C., Weber, G., Bianchi, C. & Chiumello, G. (1999) Bone density and bone metabolism are normal after long-term gluten-free diet in young celiac patients. *The American Journal of Gastroenterology.* 94(2) pp.398-403.

Moreno, M., Cebolla, Á, Muñoz-Suano, A., Carrillo-Carrion, C., Comino, I., Pizarro, Á, León, F., Rodríguez-Herrera, A. & Sousa, C. (2017) Detection of gluten immunogenic peptides in the urine of patients with coeliac disease reveals transgressions in the gluten-free diet and incomplete mucosal healing. *Gut.* 66(2) pp.250-257.

Morse, J.M. & Field, P. (1995) *Nursing Research: The Application of Qualitative Approaches.* Nelson Thornes.

Moum, T. (1998) Mode of administration and interviewer effects in self-reported symptoms of anxiety and depression. *Social Indicators Research.* 45(1-3) pp.279-318.

Muhammad, H., Reeves, S. & Jeanes, Y. (2019) Identifying and improving adherence to the gluten-free diet in people with coeliac disease. *Proceedings of the Nutrition Society.* pp.1-8. doi:10.1017/S002966511800277X

Muhammad, H. (2013) *An Assessment of Demographics and Dietary Compliance in Mixed Leicestershire Cohort using Validated Questionnaire in Patients with Coeliac Diseases (LEVANT).* Roehampton Universirty, London.

Muhammad, H., Reeves, S., Ishaq, S., Mayberry, J. & Jeanes, Y.M. (2017) Adherence to a gluten free diet is associated with receiving gluten free foods on prescription and understanding food labelling. *Nutrients.* 9(7) pp.705.

Muhammad, H., Reeves, S., Ishaq, S., Mayberry, J. and Jeanes, Y., 2018. PWE-100 Challenges in adhering to a gluten free diet in different ethnic groups. https://gut.bmj.com/content/67/Suppl_1/A168.1.abstract (Accessed: 19 February 2019).

Muhammad, H., Reeves, S., Ishaq, S., Mayberry, J. and Jeanes, Y., 2019. Qualitative interviews to explore patient preference for healthcare led interventions. Coeliac UK conference, Royal College of Physicians, Regent's Park, London. Friday 29 March, 2019. https://www.coeliac.org.uk/document-library/5729-research-conference-2019-posters-11-20/?return=/campaigns-and-research/our-research-conference/research-conference-2019/ (Accessed: 19 February 2019).

Mukherjee, R., Egbuna, I., Brar, P., Hernandez, L., McMahon, D.J., Shane, E.J., Bhagat, G. & Green, P.H. (2010) Celiac disease: Similar presentations in the elderly and young adults. *Digestive Diseases and Sciences.* 55(11) pp.3147-3153.

Mumford, D.B., Whitehouse, A.M. & Platts, M. (1991) Sociocultural correlates of eating disorders among asian schoolgirls in bradford. *The British Journal of Psychiatry.* 158(2) pp.222-228.

Murage, M.J., Tongbram, V., Feldman, S.R., Malatestinic, W.N., Larmore, C.J., Muram, T.M., Burge, R.T., Bay, C., Johnson, N. & Clifford, S. (2018) Medication adherence and persistence in patients with rheumatoid arthritis, psoriasis, and psoriatic arthritis: A systematic literature review. *Patient Preference and Adherence.* 12pp.1483.

Murray, J.A., Van Dyke, C., Plevak, M.F., Dierkhising, R.A., Zinsmeister, A.R. & Melton, L.J. (2003a) Trends in the identification and clinical features of celiac disease in a north american community, 1950–2001. *Clinical Gastroenterology and Hepatology.* 1(1) pp.19-27.

Murray, J.A., Van Dyke, C., Plevak, M.F., Dierkhising, R.A., Zinsmeister, A.R. & Melton, L.J.,3rd (2003b) Trends in the identification and clinical features of celiac disease in a north american community, 1950-2001. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association.* 1(1) pp.19-27.

Murray, J.A., Watson, T., Clearman, B. & Mitros, F. (2004) Effect of a gluten-free diet on gastrointestinal symptoms in celiac disease. *The American Journal of Clinical Nutrition.* 79(4) pp.669-673.

Mustalahti, K., Lohiniemi, S., Collin, P., Vuolteenaho, N., Laippala, P. & Maki, M. (2002) Gluten-free diet and quality of life in patients with screen-detected celiac disease. *Effective Clinical Practice.* 5(3) pp.105-113.

Mustalahti, K., Catassi, C., Reunanen, A., Fabiani, E., Heier, M., McMillan, S., Murray, L., Metzger, M.H., Gasparin, M., Bravi, E., Maki, M. & Coeliac EU Cluster, Project Epidemiology (2010) The prevalence of celiac disease in europe: Results of a centralized, international mass screening project. *Annals of Medicine.* 42(8) pp.587-595.

Nachman, F., Maurino, E., Vazquez, H., Sfoggia, C., Gonzalez, A., Gonzalez, V., del Campo, M.P., Smecuol, E., Niveloni, S. & Sugai, E. (2009) Quality of life in celiac disease patients: Prospective analysis on the importance of clinical severity at diagnosis and the impact of treatment. *Digestive and Liver Disease.* 41(1) pp.15-25.

Nakash, R.A., Hutton, J.L., Jørstad-Stein, E.C., Gates, S. & Lamb, S.E. (2006) Maximising response to postal questionnaires–a systematic review of randomised trials in health research. *BMC Medical Research Methodology.* 6(1) pp.5.

Namvarasl, B. & Chakravarty, A. (2018) Dietary behaviour and physical activity level of college students in varanasi, india. *International Journal of Research.* 5(12) pp.4627-4632.

Natarajan, S., Santa Ana, E.J., Liao, Y., Lipsitz, S.R. & McGee, D.L. (2009) Effect of treatment and adherence on ethnic differences in blood pressure control among adults with hypertension. *Annals of Epidemiology.* 19(3) pp.172-179.

Nazareth, S., Lebwohl, B., Tennyson, C.A., Simpson, S., Greenlee, H. & Green, P.H. (2015) Dietary supplement use in patients with celiac disease in the united states. *Journal of Clinical Gastroenterology.* 49(7) pp.577-581.

NHS (2018a) *NHS England, Department of Health & Social Care Availability of Gluten-Free Food on Prescription in Primary Care.* Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/753734/impact-assessment-availability-of-gluten-free-food-on-prescription.pdf . (Accessed: 19 February 2019).

NHS (2018b) *Prescribing Gluten-Free Foods in Primary Care: Guidance for CCG.* Available at: https://www.england.nhs.uk/wp-content/uploads/2018/11/prescribing-gluten-free-foods-primary-care-guidance-for-ccgs.pdf . (Accessed: 19 February 2019).

Norris, J.M., Barriga, K., Hoffenberg, E.J., Taki, I., Miao, D., Haas, J.E., Emery, L.M., Sokol, R.J., Erlich, H.A. & Eisenbarth, G.S. (2005) Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. *Jama.* 293(19) pp.2343-2351.

Norström, F., Lindholm, L., Sandström, O., Nordyke, K. & Ivarsson, A. (2011) Delay to celiac disease diagnosis and its implications for health-related quality of life. *BMC Gastroenterology.* 11(1) pp.118.

Nousia-Arvanitakis, S., Karagiozoglou-Lamboudes, T., Aggouridaki, C., Malaka-Lambrellis, E., Galli-Tsinopoulou, A. & Xefteri, M. (1999) Influence of jejunal morphology changes on exocrine pancreatic function in celiac disease. *Journal of Pediatric Gastroenterology and Nutrition.* 29(1) pp.81-85.

NSHA, 2. (2016) *Formal Consultation Report : The Future of Gluten-Free Foods on NHS Prescription Across South Nottinghamshire.* Available at: http://www.nottinghamnortheastccg.nhs.uk/wp-content/uploads/2016/03/Final-Gluten-Free-Consultation-Report.pdf . (Accessed: 19 February 2019).

O'Grady, J.G., Stevens, F.M., Harding, B., O'Gorman, T., McNicholl, B. & McCarthy, C. (1984) Hyposplenism and gluten-sensitive enteropathy. *Natural History, Incidence, and Relationship to Diet and Small Bowel Morphology.Gastroenterology.* 87(6) pp.1326-1331.

Oldenburger, I.B., Wolters, V.M., Kardol-Hoefnagel, T., Houwen, R.H. & Otten, H.G. (2018) Serum intestinal fatty acid–binding protein in the noninvasive diagnosis of celiac disease. *Apmis.* 126(3) pp.186-190.

Oliver, J.W., Kravitz, R.L., Kaplan, S.H. & Meyers, F.J. (2001) Individualized patient education and coaching to improve pain control among cancer outpatients. *Journal of Clinical Oncology.* 19(8) pp.2206-2212.

Oliver, M.I., Pearson, N., Coe, N. & Gunnell, D. (2005) Help-seeking behaviour in men and women with common mental health problems: Cross-sectional study. *The British Journal of Psychiatry : The Journal of Mental Science.* 186pp.297-301.

Olmos, M., Antelo, M., Vazquez, H., Smecuol, E., Maurino, E. & Bai, J. (2008) Systematic review and meta-analysis of observational studies on the prevalence of fractures in coeliac disease. *Digestive and Liver Disease.* 40(1) pp.46-53.

Olsson, C., Hörnell, A., Ivarsson, A. & Sydner, Y.M. (2008) The everyday life of adolescent coeliacs: Issues of importance for compliance with the gluten-free diet. *Journal of Human Nutrition and Dietetics.* 21(4) pp.359-367.

Olsson, C., Lyon, P., Hörnell, A., Ivarsson, A. & Sydner, Y.M. (2009) Food that makes you different: The stigma experienced by adolescents with celiac disease. *Qualitative Health Research.* 19(7) pp.976-984.

Ondrejka, S. & Jagadeesh, D. (2016) Enteropathy-associated T-cell lymphoma. *Current Hematologic Malignancy Reports.* 11(6) pp.504-513.

O'Neill, J. (2000) SMART goals, SMART schools. *Educational Leadership.* 57(5) pp.46-50.

O'neill, T., Felsenberg, D., Varlow, J., Cooper, C., Kanis, J. & Silman, A. (1996) The prevalence of vertebral deformity in european men and women: The european vertebral osteoporosis study. *Journal of Bone and Mineral Research.* 11(7) pp.1010-1018.

Ontiveros, N., López-Gallardo, J.A., Vergara-Jiménez, M.J. & Cabrera-Chávez, F. (2015) Self-reported prevalence of symptomatic adverse reactions to gluten and adherence to gluten-free diet in an adult mexican population. *Nutrients.* 7(7) pp.6000-6015.

Opdenakker, R. (2006) Advantages and disadvantages of four interview techniques in qualitative research. In: *Forum Qualitative Sozialforschung/Forum: Qualitative Social Research.*

Oppenheimer, S., Krispin, O., Levy, S., Ozeri, M. & Apter, A. (2018) The impact of coping patterns and chronic health conditions on health-related quality of life among children and adolescents. *European Journal of Pediatrics.* 177(6) pp.935-943.

Orfanos, P., Naska, A., Trichopoulos, D., Slimani, N., Ferrari, P., van Bakel, M., Deharveng, G., Overvad, K., Tjønneland, A. & Halkjær, J. (2007) Eating out of home and its correlates in 10 european countries. the european prospective investigation into cancer and nutrition (EPIC) study. *Public Health Nutrition.* 10(12) pp.1515-1525.

OSHA, 2. (2012) Available at: http://www.oxfordmail.co.uk/news/9476469.Gluten_free__ban__may_save___350_000/ . (Accessed: 19 February 2019).

Osterberg, L. & Blaschke, T. (2005) Adherence to medication. *New England Journal of Medicine.* 353(5) pp.487-497.

Oxentenko, A.S., Grisolano, S.W., Murray, J.A., Burgart, L.J., Dierkhising, R.A. & Alexander, J.A. (2002) The insensitivity of endoscopic markers in celiac disease. *The American Journal of Gastroenterology.* 97(4) pp.933.

Paavola, A., Kurppa, K., Ukkola, A., Collin, P., Lähdeaho, M., Huhtala, H., Mäki, M. & Kaukinen, K. (2012) Gastrointestinal symptoms and quality of life in screen-detected celiac disease. *Digestive and Liver Disease.* 44(10) pp.814-818.

Paez, M.A., Gramelspacher, A.M., Sinacore, J., Winterfield, L. & Venu, M. (2017) Delay in diagnosis of celiac disease in patients without gastrointestinal complaints. *The American Journal of Medicine.*

Panagiotou, S. & Kontogianni, M. (2017) The economic burden of gluten-free products and gluten-free diet: A cost estimation analysis in greece. *Journal of Human Nutrition and Dietetics.* 30(6) pp.746-752.

Parry, J. & Acharya, C. (2010) Celiac crisis in an older man. *Journal of the American Geriatrics Society.* 58(9) pp.1818-1819.

Passananti, V., Santonicola, A., Bucci, C., Andreozzi, P., Ranaudo, A., Di Giacomo, D.V. & Ciacci, C. (2012) Bone mass in women with celiac disease: Role of exercise and gluten-free diet. *Digestive and Liver Disease.* 44(5) pp.379-383.

Paterson, B. & Bramadat, I.J. (1992) Use of the preinterview in oral history. *Qualitative Health Research.* 2(1) pp.99-115.

Patey-Mariaud De Serre, N., Cellier, C., Jabri, B., Delabesse, E., Verkarre, V., Roche, B., Lavergne, A., Briere, J., Mauvieux, L. & Leborgne, M. (2000) Distinction between coeliac disease and refractory sprue: A simple immunohistochemical method. *Histopathology.* 37(1) pp.70-77.

Patton, M.Q. (2005) *Qualitative Research.* Wiley Online Library.

Pazianas, M., Butcher, G.P., Subhani, J.M., Finch, P.J., Ang, L., Collins, C., Heaney, R.P., Zaidi, M. & Maxwell, J.D. (2005) Calcium absorption and bone mineral density in celiacs after long term treatment with gluten-free diet and adequate calcium intake. *Osteoporosis International : A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 16(1) pp.56-63.

Peach, C. (2006) South asian migration and settlement in great britain, 1951–2001. *Contemporary South Asia.* 15(2) pp.133-146.

Pekki, H., Kurppa, K., Mäki, M., Huhtala, H., Laurila, K., Ilus, T. & Kaukinen, K. (2017) Performing routine follow-up biopsy 1 year after diagnosis does not affect long-term outcomes in coeliac disease. *Alimentary Pharmacology & Therapeutics.* 45(11) pp.1459-1468.

Pekki, H., Kaukinen, K., Ilus, T., Mäki, M., Huhtala, H., Laurila, K. & Kurppa, K. (2018) Long-term follow-up in adults with coeliac disease: Predictors and effect on health outcomes. *Digestive and Liver Disease.*

Penneys, N.S. & Glaser, D.A. (1999) The incidence of cancellation and nonattendance at a dermatology clinic. *Journal of the American Academy of Dermatology.* 40(5) pp.714-718.

Petersen, J., Montserrat, V., Mujico, J.R., Loh, K.L., Beringer, D.X., van Lummel, M., Thompson, A., Mearin, M.L., Schweizer, J. & Kooy-Winkelaar, Y. (2014) T-cell receptor recognition of HLA-DQ2–gliadin complexes associated with celiac disease. *Nature Structural & Molecular Biology.* 21(5) pp.480-488.

Petrovski, G., Zivkovic, M. & Stratrova, S.S. (2015) Social media and diabetes: Can facebook and skype improve glucose control in patients with type 1 diabetes on pump therapy? one-year experience. *Diabetes Care.* 38(4) pp.e51-2.

Pfaender, M., D'Souza, W.J., Trost, N., Litewka, L., Paine, M. & Cook, M. (2004) Visual disturbances representing occipital lobe epilepsy in patients with cerebral calcifications and coeliac disease: A case series. *Journal of Neurology, Neurosurgery, and Psychiatry.* 75(11) pp.1623-1625.

Picarelli, A., Di Tola, M., Sabbatella, L., Vetrano, S., Anania, M.C., Spadaro, A., Sorgi, M.L. & Taccari, E. (2003) Anti-tissue transglutaminase antibodies in arthritic patients: A disease-specific finding? *Clinical Chemistry.* 49(12) pp.2091-2094.

Pietschmann, P., Rauner, M., Sipos, W. & Kerschan-Schindl, K. (2009) Osteoporosis: An age-related and gender-specific disease--a mini-review. *Gerontology.* 55(1) pp.3-12.

Pietzak, M.M. (2005) Follow-up of patients with celiac disease: Achieving compliance with treatment. *Gastroenterology.* 128(4 Suppl 1) pp.S135-41.

Pink, I. & Creamer, B. (1967) Response to a gluten-free diet of patients with the coeliac syndrome. *The Lancet.* 289(7485) pp.300-304.

Pittschieler, K. & Ladinser, B. (1996) Coeliac disease: Screened by a new strategy. *Acta Paediatrica.* 85(s412) pp.42-45.

Planas, R., Pujol-Autonell, I., Ruiz, E., Montraveta, M., Cabre, E., Lucas-Martin, A., Pujol-Borrell, R., Martinez-Caceres, E. & Vives-Pi, M. (2011) Regenerating gene iα is a biomarker for diagnosis and monitoring of celiac disease: A preliminary study. *Translational Research.* 158(3) pp.140-145.

Playford, E.D., Siegert, R., Levack, W. & Freeman, J. (2009) Areas of consensus and controversy about goal setting in rehabilitation: A conference report. *Clinical Rehabilitation.* 23(4) pp.334-344.

Plenge, R.M. (2010) Unlocking the pathogenesis of celiac disease. *Nature Genetics.* 42(4) pp.281.

Plotkin, G.R. & Isselbacher, K.J. (1964) Secondary disaccharidase deficiency in adult celiac disease (nontropical sprue) and other malabsorption states. *New England Journal of Medicine.* 271(20) pp.1033-1037.

Pourhoseingholi, M.A., Rostami-Nejad, M., Barzegar, F., Rostami, K., Volta, U., Sadeghi, A., Honarkar, Z., Salehi, N., Asadzade-Aghdaei, H. & Baghestani, A.R. (2017) Economic burden made celiac disease an expensive and challenging condition for iranian patients. *Gastroenterology and Hepatology from Bed to Bench.*

Poushter, J. (2016) Smartphone ownership and internet usage continues to climb in emerging economies. *Pew Research Center.*

Pozo-Rubio, T., De Palma, G., Mujico, J.R., Olivares, M., Marcos, A., Acuña, M.D., Polanco, I., Sanz, Y. & Nova, E. (2013) Influence of early environmental factors on lymphocyte subsets and gut microbiota in infants at risk of celiac disease; the PROFICEL study. *Nutricion Hospitalaria.* 28(2) .

Pratesi, C., Häuser, W., Uenishi, R., Selleski, N., Nakano, E., Gandolfi, L., Pratesi, R. & Zandonadi, R. (2018) Quality of life of celiac patients in brazil: Questionnaire translation, cultural adaptation and validation. *Nutrients.* 10(9) pp.1167.

Pratesi, R., Modelli, I., Martins, R., Almeida, P. & Gandolfi, L. (2003) Celiac disease and epilepsy: Favorable outcome in a child with difficult to control seizures. *Acta Neurologica Scandinavica.* 108(4) pp.290-293.

Price, E.L., Pérez-Stable, E.J., Nickleach, D., López, M. & Karliner, L.S. (2012) Interpreter perspectives of in-person, telephonic, and videoconferencing medical interpretation in clinical encounters. *Patient Education and Counseling.* 87(2) pp.226-232.

Prochaska, J.O., Butterworth, S., Redding, C.A., Burden, V., Perrin, N., Leo, M., Flaherty-Robb, M. & Prochaska, J.M. (2008) Initial efficacy of MI, TTM tailoring and HRI's with multiple behaviors for employee health promotion. *Preventive Medicine.* 46(3) pp.226-231.

Puccetti, A., Saverino, D., Opri, R., Gabrielli, O., Zanoni, G., Pelosi, A., Fiore, P.F., Moretta, F., Lunardi, C. & Dolcino, M. (2018) Immune response to rotavirus and gluten sensitivity. *Journal of Immunology Research.* 2018.

Qiu, A., Jansen, M., Sakaris, A., Min, S.H., Chattopadhyay, S., Tsai, E., Sandoval, C., Zhao, R., Akabas, M.H. & Goldman, I.D. (2006) Identification of an intestinal folate transporter and the molecular basis for hereditary folate malabsorption. *Cell.* 127(5) pp.917-928.

Qu, S.Q. & Dumay, J. (2011) The qualitative research interview. *Qualitative Research in Accounting & Management.* 8(3) pp.238-264.

Rajpoot, P., Sharma, A., Harikrishnan, S., Baruah, B.J., Ahuja, V. & Makharia, G.K. (2015) Adherence to gluten-free diet and barriers to adherence in patients with celiac disease. *Indian Journal of Gastroenterology.* 34(5) pp.380-386.

Rajpoot, P. & Makharia, G.K. (2013) Problems and challenges to adaptation of gluten free diet by indian patients with celiac disease. *Nutrients.* 5(12) pp.4869-4879.

Ramachandran, B.S. & Jacob, M. (2016) Celiac disease in kerala. *Indian Journal of Gastroenterology.* 35(6) pp.492-494.

Ramakrishna, B., Makharia, G.K., Chetri, K., Dutta, S., Mathur, P., Ahuja, V., Amarchand, R., Balamurugan, R., Chowdhury, S.D. & Daniel, D. (2016) Prevalence of adult celiac disease in india: Regional variations and associations. *The American Journal of Gastroenterology.* 111(1) pp.115-123.

Ramírez-Cervantes, K.L., Remes-Troche, J.M., del Pilar Milke-García, M., Romero, V. & Uscanga, L.F. (2015) Characteristics and factors related to quality of life in mexican mestizo patients with celiac disease. *BMC Gastroenterology.* 15(1) pp.4.

Ramirez-Cervantes, K.L., Romero-Lopez, A.V., Nunez-Alvarez, C.A. & Uscanga-Dominguez, L.F. (2016) Adherence to a gluten-free diet in mexican subjects with gluten-related disorders: A high prevalence of inadvertent gluten intake. *Revista De Investigacion Clinica; Organo Del Hospital De Enfermedades De La Nutricion.* 68(5) pp.229-234.

Rampertab, S.D., Pooran, N., Brar, P., Singh, P. & Green, P.H. (2006) Trends in the presentation of celiac disease. *The American Journal of Medicine.* 119(4) pp.355. e9-355. e14.

Randomiser (2016) *Generate Numbers.* Available at: https://www.randomizer.org/ . (Accessed: 19 February 2019).

Rankin, S.H., Stallings, K.D. & London, F. (2005) *Patient Education in Health and Illness.* Lippincott Williams & Wilkins.

Rashid, M. & Khan, A.G. (2009) Celiac disease in pakistan: Challenges and opportunities. *Journal of Ayub Medical College, Abbottabad : JAMC.* 21(3) pp.1-2.

Raynor, D. (2018) Do patients see, read and retain the new mandatory medicines information leaflets? *Pathophysiology.* 14pp.00.

Redman, B.K. (2005) The ethics of self-management preparation for chronic illness. *Nursing Ethics.* 12(4) pp.360-369.

Reilly, N.R., Fasano, A. & Green, P.H. (2012) Presentation of celiac disease. *Gastrointestinal Endoscopy Clinics of North America.* 22(4) pp.613-621.

Reilly, N.R. (2016) The gluten-free diet: Recognizing fact, fiction, and fad. *The Journal of Pediatrics.* 175pp.206-210.

REP (2018) *Data Exploration Portal.* Available at: http://www.rochesterproject.org/portal/ . (Accessed: 19 February 2019).

Rewers, M. (2005) Epidemiology of celiac disease: What are the prevalence, incidence, and progression of celiac disease? *Gastroenterology.* 128(4) pp.S47-S51.

Richards, D. (2007) How to increase response rates to postal questionnaires. *Evidence-Based Dentistry.* 8(2) pp.53-54.

Richardson, J.T. (2005) Instruments for obtaining student feedback: A review of the literature. *Assessment & Evaluation in Higher Education.* 30(4) pp.387-415.

Richardson, J.T. (2004) Methodological issues in questionnaire-based research on student learning in higher education. *Educational Psychology Review.* 16(4) pp.347-358.

Riddle, M.S., Murray, J.A. & Porter, C.K. (2012) The incidence and risk of celiac disease in a healthy US adult population. *The American Journal of Gastroenterology.* 107(8) pp.1248-1255.

Ring Jacobsson, L., Friedrichsen, M., Göransson, A. & Hallert, C. (2012) Does a coeliac school increase psychological well-being in women suffering from coeliac disease, living on a gluten-free diet? *Journal of Clinical Nursing.* 21(5-6) pp.766-775.

Robert, M.E. (2005) Gluten sensitive enteropathy and other causes of small intestinal lymphocytosis. In: *Seminars in Diagnostic Pathology.* Elsevier. pp.284-294.

Roberts, P. & Priest, H. (2006) Reliability and validity in research. *Nursing Standard (Royal College of Nursing (Great Britain) : 1987).* 20(44) pp.41-45.

Robson, C. (2002) Real world research: A resource for social scientists and practitioner. *Adapting Open Innovation in ICT Ecosystem Dynamics References Real World Research: A Resource for Social Scientists and Practitioner.* pp.270.

Rodrigues, M., Yonaminez, G.H. & Satiro, C.A. (2018) Rate and determinants of non-adherence to a gluten-free diet and nutritional status assessment in children and adolescents with celiac disease in a

tertiary brazilian referral center: A cross-sectional and retrospective study. *BMC Gastroenterology.* 18(1) pp.15.

Rodríguez Almagro, J., Hernández Martínez, A., Solano Ruiz, M.C. & Siles González, J. (2017) Using mixed-methods research to study the quality of life of coeliac women. *Journal of Clinical Nursing.* 26(7-8) pp.1119-1130.

Rokkas, T. & Niv, Y. (2012) The role of video capsule endoscopy in the diagnosis of celiac disease: A meta-analysis. *European Journal of Gastroenterology & Hepatology.* 24(3) pp.303-308.

Roll, K., Stargardt, T. & Schreyögg, J. (2012) Effect of type of insurance and income on waiting time for outpatient care. *The Geneva Papers on Risk and Insurance Issues and Practice.* 37(4) pp.609-632.

Rondonotti, E., Spada, C., Cave, D., Pennazio, M., Riccioni, M.E., De Vitis, I., Schneider, D., Sprujevnik, T., Villa, F. & Langelier, J. (2007) Video capsule enteroscopy in the diagnosis of celiac disease: A multicenter study. *The American Journal of Gastroenterology.* 102(8) pp.1624-1631.

Roos, S., Hellstrom, I., Hallert, C. & Wilhelmsson, S. (2013) Everyday life for women with celiac disease. *Gastroenterology Nursing : The Official Journal of the Society of Gastroenterology Nurses and Associates.* 36(4) pp.266-273.

Root, D. & Blismas, N. (2003) Increasing questionnaire responses from industry: Practices surrounding the use of postal questionnaires. *Management.* 2pp.623-631.

Rose, C. & Howard, R. (2014) Living with coeliac disease: A grounded theory study. *Journal of Human Nutrition and Dietetics : The Official Journal of the British Dietetic Association.* 27(1) pp.30-40.

Rosen, A., Emmelin, M., Carlsson, A., Hammarroth, S., Karlsson, E. & Ivarsson, A. (2011) Mass screening for celiac disease from the perspective of newly diagnosed adolescents and their parents: A mixed-method study. *BMC Public Health.* 11pp.822-2458-11-822.

Rostami, K., Bold, J., Parr, A. & Johnson, M.W. (2017) *Gluten-Free Diet Indications, Safety, Quality, Labels, and Challenges.*

Rostom, A., Dubé, C., Cranney, A., Saloojee, N., Sy, R., Garritty, C., Sampson, M., Zhang, L., Yazdi, F. & Mamaladze, V. (2004) Celiac disease. *Evid Rep Technol Assess (Summ).* 104(104) pp.1-6.

Rubin, H.R., Gandek, B., Rogers, W.H., Kosinski, M., McHorney, C.A. & Ware, J.E. (1993) Patients' ratings of outpatient visits in different practice settings: Results from the medical outcomes study. *Jama.* 270(7) pp.835-840.

Rubin, H.J. & Rubin, I.S. (2011) *Qualitative Interviewing: The Art of Hearing Data.* Sage.

Rubio-Tapia, A., Hill, I.D., Kelly, C.P., Calderwood, A.H. & Murray, J.A. (2013) ACG clinical guidelines: Diagnosis and management of celiac disease. *The American Journal of Gastroenterology.* 108(5) pp.656-676.

Rubio-Tapia, A., Ludvigsson, J.F., Brantner, T.L., Murray, J.A. & Everhart, J.E. (2012) The prevalence of celiac disease in the united states. *The American Journal of Gastroenterology.* 107(10) pp.1538-1544.

Rubio-Tapia, A., Kyle, R.A., Kaplan, E.L., Johnson, D.R., Page, W., Erdtmann, F., Brantner, T.L., Kim, W.R., Phelps, T.K., Lahr, B.D., Zinsmeister, A.R., Melton, L.J.,3rd & Murray, J.A. (2009) Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology.* 137(1) pp.88-93.

Rubio-Tapia, A., Rahim, M.W., See, J.A., Lahr, B.D., Wu, T.T. & Murray, J.A. (2010) Mucosal recovery and mortality in adults with celiac disease after treatment with a gluten-free diet. *The American Journal of Gastroenterology.* 105(6) pp.1412-1420.

Rübsamen, N., Akmatov, M.K., Castell, S., Karch, A. & Mikolajczyk, R.T. (2017) Comparison of response patterns in different survey designs: A longitudinal panel with mixed-mode and online-only design. *Emerging Themes in Epidemiology.* 14(1) pp.4.

Rueda, S., Park-Wyllie, L.Y., Bayoumi, A., Tynan, A., Antoniou, T., Rourke, S. & Glazier, R. (2006) Patient support and education for promoting adherence to highly active antiretroviral therapy for HIV/AIDS. *The Cochrane Library.*

Rujner, J., Socha, J., Syczewska, M., Wojtasik, A., Kunachowicz, H. & Stolarczyk, A. (2004) Magnesium status in children and adolescents with coeliac disease without malabsorption symptoms. *Clinical Nutrition.* 23(5) pp.1074-1079.

Ryan, D., Pelly, F. & Purcell, E. (2016) The activities of a dietitian-led gastroenterology clinic using extended scope of practice. *BMC Health Services Research.* 16(1) pp.604.

Sabaté, E. (2003) *Adherence to Long-Term Therapies: Evidence for Action.* World Health Organization.

Sachdev, A., Srinivasan, V., Maheswary, S., Mohan, H., Ashish, B. & Singh, L.S. (2002) Adult onset celiac disease in north india. *Tropical Gastroenterology : Official Journal of the Digestive Diseases Foundation.* 23(3) pp.117-119.

Sainsbury, A., Sanders, D.S. & Ford, A.C. (2013) Prevalence of irritable bowel syndrome–type symptoms in patients with celiac disease: A meta-analysis. *Clinical Gastroenterology and Hepatology.* 11(4) pp.359-365. e1.

Sainsbury, K., Halmos, E.P., Knowles, S., Mullan, B. & Tye-Din, J.A. (2018) Maintenance of a gluten free diet in coeliac disease: The roles of self-regulation, habit, psychological resources, motivation, support, and goal priority. *Appetite.* 125pp.356-366.

Sainsbury, K. & Marques, M.M. (2017) The relationship between gluten free diet adherence and depressive symptoms in adults with coeliac disease: A systematic review with meta-analysis. *Appetite.*

Sainsbury, K., Mullan, B. & Sharpe, L. (2015) Predicting intention and behaviour following participation in a theory-based intervention to improve gluten free diet adherence in coeliac disease. *Psychology & Health.* 30(9) pp.1063-1074.

Sainsbury, K., Mullan, B. & Sharpe, L. (2014) Dissemination of an online theory-based intervention to improve gluten-free diet adherence in coeliac disease: The relationship between acceptability, effectiveness, and attrition. *International Journal of Behavioral Medicine.*

Sainsbury, K., Mullan, B. & Sharpe, L. (2013a) Gluten free diet adherence in coeliac disease. the role of psychological symptoms in bridging the intention-behaviour gap. *Appetite.* 61(1) pp.52-58.

Sainsbury, K., Mullan, B. & Sharpe, L. (2013b) A randomized controlled trial of an online intervention to improve gluten-free diet adherence in celiac disease. *The American Journal of Gastroenterology.* 108(5) pp.811-817.

Sainsbury, K., Mullan, B. & Sharpe, L. (2013c) Reduced quality of life in coeliac disease is more strongly associated with depression than gastrointestinal symptoms. *Journal of Psychosomatic Research.* 75(2) pp.135-141.

Saleem, N., Ali, S., Ahmed, T.A., Iqbal, M. & Bashir, M. (2013) HLA-DR alleles among pakistani patients of coeliac disease. *JPMA.the Journal of the Pakistan Medical Association.* 63(10) pp.1271-1274.

Salim Silva, M., Smith, W.T. & Bammer, G. (2002) Telephone reminders are a cost effective way to improve responses in postal health surveys. *Journal of Epidemiology and Community Health.* 56(2) pp.115-118.

Samasca, G., Sur, G., Lupan, I. & Deleanu, D. (2014) Gluten-free diet and quality of life in celiac disease. *Gastroenterology and Hepatology from Bed to Bench.* 7(3) pp.139.

Sanchez-Munoz, L.B., Santon, A., Cano, A., Lopez, A., Almeida, J., Orfao, A., Escribano, L. & Roy, G. (2008) Flow cytometric analysis of intestinal intraepithelial lymphocytes in the diagnosis of refractory celiac sprue. *European Journal of Gastroenterology & Hepatology.* 20(5) pp.478-487.

Sanders, D.S., Carter, M.J., Hurlstone, D.P., Pearce, A., Ward, A.M., McAlindon, M.E. & Lobo, A.J. (2001) Association of adult coeliac disease with irritable bowel syndrome: A case-control study in patients fulfilling ROME II criteria referred to secondary care. *The Lancet.* 358(9292) pp.1504-1508.

Sanders, D.S., Patel, D., Stephenson, T.J., Ward, A.M., McCloskey, E.V., Hadjivassiliou, M. & Lobo, A.J. (2003) A primary care cross-sectional study of undiagnosed adult coeliac disease. *European Journal of Gastroenterology & Hepatology.* 15(4) pp.407-413.

Saris, W.E. & Gallhofer, I.N. (2007) *Design, Evaluation, and Analysis of Questionnaires for Survey Research.* John Wiley & Sons.

Sathiyasekeran, M. & Shivbalan, S. (2005) Celiac disease in chennai. *Indian Pediatrics.* 42(11) pp.1171.

Saturni, L., Ferretti, G. & Bacchetti, T. (2010) The gluten-free diet: Safety and nutritional quality. *Nutrients.* 2(1) pp.16-34.

Sayed, S.K., Imam, H., Mahran, A.M. & Refaiy, A.M. (2012) Diagnostic utility of deamidated gliadin peptide antibody in celiac disease compared to anti-tissue transglutaminase and IgA–endomysium antibodies. *Egypt J Immunol.* 19pp.41-52.

Schilling, K.W., Yohannessen, K. & Araya, M. (2018) Perception of following gluten-free diet and adherence to treatment in pediatric patients with celiac disease. *Revista Chilena De Pediatria.* 89(2) pp.216-223.

Schmitz, J. (1997) Lack of oats toxicity in coeliac disease. *BMJ (Clinical Research Ed.).* 314(7075) pp.159-160.

Schulz, R., Bookwala, J., Knapp, J.E., Scheier, M. & Williamson, G.M. (1996) Pessimism, age, and cancer mortality. *Psychology and Aging.* 11pp.304-309.

Schuman, H. & Presser, S. (1996) *Questions and Answers in Attitude Surveys: Experiments on Question Form, Wording, and Context.* Sage.

Schuppan, D. & Junker, Y. (2007) Turning swords into plowshares: Transglutaminase to detoxify gluten. *Gastroenterology.* 133(3) pp.1025-1028.

Schwarzer, R. (2014) *Self-Efficacy: Thought Control of Action.* Taylor & Francis.

Sdepanian, V.L., Morais, M.B.d. & Fagundes-Neto Ulysses (2001) Celiac disease: Evaluation of compliance to a gluten-free diet and knowledge of the disease in celiac patients registered at the brazilian celiac association (BCA). *Arquivos De Gastroenterologia.* 38(4) pp.232-239.

See, J. & Murray, J.A. (2006) Gluten-free diet: The medical and nutrition management of celiac disease. *Nutrition in Clinical Practice : Official Publication of the American Society for Parenteral and Enteral Nutrition.* 21(1) pp.1-15.

Senapati, S., Gutierrez-Achury, J., Sood, A., Midha, V., Szperl, A., Romanos, J., Zhernakova, A., Franke, L., Alonso, S. & Thelma, B. (2015) Evaluation of european coeliac disease risk variants in a north indian population. *European Journal of Human Genetics.* 23(4) pp.530-535.

Seng, E.K., Rains, J.A., Nicholson, R.A. & Lipton, R.B. (2015) Improving medication adherence in migraine treatment. *Current Pain and Headache Reports.* 19(6) pp.24.

Shah, S., Akbari, M., Vanga, R., Kelly, C.P., Hansen, J., Theethira, T., Tariq, S., Dennis, M. & Leffler, D.A. (2014) Patient perception of treatment burden is high in celiac disease compared with other common conditions. *The American Journal of Gastroenterology.* 109(9) pp.1304.

Shah, S. & Leffler, D. (2010) Celiac disease: An underappreciated issue in women's health. *Women's Health.* 6(5) pp.753-766.

Shalaby, S.A., Sayed, M.M., Ibrahim, W.A., Abdelhakam, S.M. & Rushdy, M. (2016) The prevalence of coeliac disease in patients fulfilling rome III criteria for irritable bowel syndrome. *Arab Journal of Gastroenterology.* 17(2) pp.73-77.

Shan, L., Molberg, O., Parrot, I., Hausch, F., Filiz, F., Gray, G.M., Sollid, L.M. & Khosla, C. (2002) Structural basis for gluten intolerance in celiac sprue. *Science (New York, N.Y.).* 297(5590) pp.2275-2279.

Shanmugalakshmi, S., Balakrishnan, K., Manoharan, K. & Pitchappan, R. (2003) HLA-DRB1*,-DQB1* in piramalai kallars and yadhavas, two dravidian-speaking castes of tamil nadu, south india. *Hla.* 61(6) pp.451-464.

Sharkey, L., Corbett, G., Currie, E., Lee, J., Sweeney, N. & Woodward, J. (2013) Optimising delivery of care in coeliac disease–comparison of the benefits of repeat biopsy and serological follow-up. *Alimentary Pharmacology & Therapeutics.* 38(10) pp.1278-1291.

Sharma, M., Singh, P., Agnihotri, A., Das, P., Mishra, A., Verma, A.K., Ahuja, A., Sreenivas, V., Khadgawat, R., Gupta, S.D. & Makharia, G.K. (2013) Celiac disease: A disease with varied manifestations in adults and adolescents. *Journal of Digestive Diseases.* 14(10) pp.518-525.

Sharp, K., Walker, H. & Coppell, K.J. (2014) Coeliac disease and the gluten-free diet in new zealand: The new zealand coeliac health survey. *Nutrition & Dietetics.* 71(4) pp.223-228.

Sheldon, H., Graham, C., Pothecary, N. & Rasul, F. (2007) Increasing response rates amongst black and minority ethnic and seldom heard groups. *Europe: Picker Institute.*

Shelley Case, B.D. (2013) *Webinar: Celiac Disease, Gluten Sensitivity and the Gluten Free Diet.* Available at: https://ce.todaysdietitian.com/GlutenFreeWebinar (Accessed: 19 February 2019).

Shepherd, S.J. & Gibson, P.R. (2013) Nutritional inadequacies of the gluten-free diet in both recently-diagnosed and long-term patients with coeliac disease. *Journal of Human Nutrition and Dietetics : The Official Journal of the British Dietetic Association.* 26(4) pp.349-358.

Sher, K.S., Fraser, R.C., Wicks, A.C. & Mayberry, J.F. (1993) High risk of coeliac disease in punjabis. epidemiological study in the south asian and european populations of leicestershire. *Digestion.* 54(3) pp.178-182.

Silano, M., Volta, U., De Vincenzi, A., Dessì, M., De Vincenzi, M. & Collaborating Centers of the Italian Registry of the Complications of Coeliac Disease (2008) Effect of a gluten-free diet on the risk of

enteropathy-associated T-cell lymphoma in celiac disease. *Digestive Diseases and Sciences.* 53(4) pp.972-976.

Silano, M., Volta, U., Mecchia, A.M., Dessì, M., Di Benedetto, R. & De Vincenzi, M. (2007) Delayed diagnosis of coeliac disease increases cancer risk. *BMC Gastroenterology.* 7(1) pp.8.

Silano, M., Agostoni, C., Sanz, Y. & Guandalini, S. (2016) Infant feeding and risk of developing celiac disease: A systematic review. *BMJ Open.* 6(1) pp.e009163-2015-009163.

Silvester, J.A. & Rashid, M. (2007) Long-term follow-up of individuals with celiac disease: An evaluation of current practice guidelines. *Canadian Journal of Gastroenterology = Journal Canadien De Gastroenterologie.* 21(9) pp.557-564.

Silvester, J., Weiten, D., Graff, L., Walker, J. & Duerksen, D. (2016) Living gluten-free: Adherence, knowledge, lifestyle adaptations and feelings towards a gluten-free diet. *Journal of Human Nutrition and Dietetics.* 29(3) pp.374-382.

Silvester, J.A., Weiten, D., Graff, L.A., Walker, J.R. & Duerksen, D.R. (2016) Is it gluten-free? relationship between self-reported gluten-free diet adherence and knowledge of gluten content of foods. *Nutrition.* 32(7) pp.777-783.

Simmons, D. & Williams, R. (1997) Dietary practices among europeans and different south asian groups in coventry. *British Journal of Nutrition.* 78(1) pp.5-14.

Simpson, S. & Thompson, T. (2012) Nutrition assessment in celiac disease. *Gastrointestinal Endoscopy Clinics of North America.* 22(4) pp.797-809.

Sinclair, M., O'Toole, J., Malawaraarachchi, M. & Leder, K. (2012) Comparison of response rates and cost-effectiveness for a community-based survey: Postal, internet and telephone modes with generic or personalised recruitment approaches. *BMC Medical Research Methodology.* 12pp.132-2288-12-132.

Singh, J. & Whelan, K. (2011) Limited availability and higher cost of gluten-free foods. *Journal of Human Nutrition and Dietetics.* 24(5) pp.479-486.

Singh, M. (2011) Adherence to asthma treatment. *Asthma in Children.* pp.121.

Singh, P., Arora, S., Singh, A., Strand, T.A. & Makharia, G.K. (2016) Prevalence of celiac disease in asia: A systematic review and meta-analysis. *Journal of Gastroenterology and Hepatology.* 31(6) pp.1095-1101.

Singh, P. & Makharia, G.K. (2014) Non-classical celiac disease: Often missed. *International Journal of Celiac Disease.* 2(3) pp.76-85.

Siniscalchi, M., Iovino, P., Tortora, R., Forestiero, S., Somma, A., Capuano, L., Franzese, M., Sabbatini, F. & Ciacci, C. (2005a) Fatigue in adult coeliac disease. *Alimentary Pharmacology & Therapeutics.* 22(5) pp.489-494.

Siniscalchi, M., Iovino, P., Tortora, R., Forestiero, S., Somma, A., Capuano, L., Franzese, M.D., Sabbatini, F. & Ciacci, C. (2005b) Fatigue in adult coeliac disease. *Alimentary Pharmacology & Therapeutics.* 22(5) pp.489-494.

Skjerning, H., Hourihane, J., Husby, S. & DunnGalvin, A. (2017) A comprehensive questionnaire for the assessment of health-related quality of life in coeliac disease (CDQL). *Quality of Life Research.* 26(10) pp.2831-2850.

Smith, G. (2008) Does gender influence online survey participation?: A record-linkage analysis of university faculty online survey response behavior. *ERIC Document Reproduction Service no.ED 501717.*

Smukalla, S., Lebwohl, B., Mears, J.G., Leslie, L.A. & Green, P.H. (2014) How often do hematologists consider celiac disease in iron-deficiency anemia? results of a national survey. *Clinical Advances in Hematology & Oncology : H&O.* 12(2) pp.100-105.

Smyth, D.J., Plagnol, V., Walker, N.M., Cooper, J.D., Downes, K., Yang, J.H., Howson, J.M., Stevens, H., McManus, R. & Wijmenga, C. (2008) Shared and distinct genetic variants in type 1 diabetes and celiac disease. *New England Journal of Medicine.* 359(26) pp.2767-2777.

Sood, A., Midha, V., Sood, N., Avasthi, G. & Sehgal, A. (2006) Prevalence of celiac disease among school children in punjab, north india. *Journal of Gastroenterology and Hepatology.* 21(10) pp.1622-1625.

Sood, A., Midha, V., Sood, N., Kaushal, V. & Puri, H. (2001) Increasing incidence of celiac disease in india. *The American Journal of Gastroenterology.* 96(9) pp.2804-2805.

Sood, A., Midha, V., Sood, N. & Malhotra, V. (2003) Adult celiac disease in northern india. *Indian Journal of Gastroenterology : Official Journal of the Indian Society of Gastroenterology.* 22(4) pp.124-126.

Spatola, B.N., Kaukinen, K., Collin, P., Mäki, M., Kagnoff, M.F. & Daugherty, P. (2014) Persistence of elevated deamidated gliadin peptide antibodies on a gluten-free diet indicates nonresponsive coeliac disease. *Alimentary Pharmacology & Therapeutics.* 39(4) pp.407-417.

Sperandeo, M.P., Tosco, A., Izzo, V., Tucci, F., Troncone, R., Auricchio, R., Romanos, J., Trynka, G., Auricchio, S. & Jabri, B. (2011) Potential celiac patients: A model of celiac disease pathogenesis. *PloS One.* 6(7) pp.e21281.

Stazi, A. & Mantovani, A. (2000) A risk factor for female fertility and pregnancy: Celiac disease. *Gynecological Endocrinology.* 14(6) pp.454-463.

Stellefson, M., Chaney, B., Ochipa, K., Chaney, D., Haider, Z., Hanik, B., Chavarria, E. & Bernhardt, J.M. (2014) YouTube as a source of chronic obstructive pulmonary disease patient education: A social media content analysis. *Chronic Respiratory Disease.* 11(2) pp.61-71.

Stene, L.C., Honeyman, M.C., Hoffenberg, E.J., Haas, J.E., Sokol, R.J., Emery, L., Taki, I., Norris, J.M., Erlich, H.A. & Eisenbarth, G.S. (2006) Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: A longitudinal study. *The American Journal of Gastroenterology.* 101(10) pp.2333-2340.

Stenman, S.M., Venäläinen, J.I., Lindfors, K., Auriola, S., Mauriala, T., Kaukovirta-Norja, A., Jantunen, A., Laurila, K., Qiao, S. & Sollid, L.M. (2009) Enzymatic detoxification of gluten by germinating wheat proteases: Implications for new treatment of celiac disease. *Annals of Medicine.* 41(5) pp.390-400.

Stevens, L. & Rashid, M. (2008a) Gluten-free and regular foods: A cost comparison. *Canadian Journal of Dietetic Practice and Research.* 69(3) pp.147-150.

Stevens, L. & Rashid, M. (2008b) Gluten-free and regular foods: A cost comparison. *Canadian Journal of Dietetic Practice and Research.* 69(3) pp.147-150.

Stewart, M., Andrews, C., Urbanski, S., Beck, P. & Storr, M. (2011) The association of coeliac disease and microscopic colitis: A large population-based study. *Alimentary Pharmacology & Therapeutics.* 33(12) pp.1340-1349.

Stone, C. & Rowles, C.J. (2007) Nursing students can help support evidence-based practice on clinical nursing units. *Journal of Nursing Management.* 15(3) pp.367-370.

Stone, M., Pound, E., Pancholi, A., Farooqi, A. & Khunti, K. (2005) Empowering patients with diabetes: A qualitative primary care study focusing on south asians in leicester, UK. *Family Practice.* 22(6) pp.647-652.

Størdal, K., Bakken, I.J., Surén, P. & Stene, L.C. (2013) Epidemiology of coeliac disease and comorbidity in norwegian children. *Journal of Pediatric Gastroenterology and Nutrition.* 57(4) pp.467-471.

Strauss, A. & Corbin, J. (1990) *Basics of Qualitative Research.* Newbury Park, CA: Sage.

Sturges, J.E. & Hanrahan, K.J. (2004) Comparing telephone and face-to-face qualitative interviewing: A research note. *Qualitative Research.* 4(1) pp.107-118.

Sverker, A., Hensing, G. & Hallert, C. (2005) 'Controlled by food'–lived experiences of coeliac disease. *Journal of Human Nutrition and Dietetics.* 18(3) pp.171-180.

Sykes, L.L., Walker, R.L., Ngwakongnwi, E. & Quan, H. (2010) A systematic literature review on response rates across racial and ethnic populations. *Canadian Journal of Public Health/Revue Canadienne De Sante'E Publique.* pp.213-219.

Szczepura, A., Price, C. & Gumber, A. (2008) Breast and bowel cancer screening uptake patterns over 15 years for UK south asian ethnic minority populations, corrected for differences in socio-demographic characteristics. *BMC Public Health.* 8(1) pp.346.

Szymczak, J., Bohdanowicz-Pawlak, A., Waszczuk, E. & Jakubowska, J. (2012) Low bone mineral density in adult patients with coeliac disease. *Endokrynologia Polska.* 63(4) pp.270-276.

Taghdir, M., Honar, N., Mazloomi, S.M., Sepandi, M., Ashourpour, M. & Salehi, M. (2016) Dietary compliance in iranian children and adolescents with celiac disease. *Journal of Multidisciplinary Healthcare.* 9pp.365-370.

Tai, S.S., Nazareth, I., Haines, A. & Jowett, C. (1997) A randomized trial of the impact of telephone and recorded delivery reminders on the response rate to research questionnaires. *Journal of Public Health.* 19(2) pp.219-221.

Tajuddin, T., Razif, S., Thorne, J. & Murray, F. (2009) Clinical presentation of adult coeliac disease.

Teixeira, L.M., Nisihara, R., Utiyama, Shirley Ramos da Rosa, Bem, R.S.d., Marcatto, C., Bertolazo, M. & Carvalho, G.A.d. (2014) Screening of celiac disease in patients with autoimmune thyroid disease from southern brazil. *Arquivos Brasileiros De Endocrinologia & Metabologia.* 58(6) pp.625-629.

TekıNer, H. (2015) Aretaeus of cappadocia and his treatises on diseases. *Turk Neurosurg.* 25(3) pp.508-512.

Temple, B. & Young, A. (2004) Qualitative research and translation dilemmas. *Qualitative Research.* 4(2) pp.161-178.

Tersigni, C., Castellani, R., De Waure, C., Fattorossi, A., De Spirito, M., Gasbarrini, A., Scambia, G. & Di Simone, N. (2014) Celiac disease and reproductive disorders: Meta-analysis of epidemiologic associations and potential pathogenic mechanisms. *Human Reproduction Update.* 20(4) pp.582-593.

Thompson, T. (2009) The nutritional quality of gluten-free foods. *Gluten-Free Food Science and Technology.* pp.42e51.

Thompson, T., Lee, A.R. & Grace, T. (2010) Gluten contamination of grains, seeds, and flours in the united states: A pilot study. *Journal of the American Dietetic Association.* 110(6) pp.937-940.

Thong, E.P., Wong, P., Dev, A., Ebeling, P.R., Teede, H.J. & Milat, F. (2018) Increased prevalence of fracture and hypoglycaemia in young adults with concomitant type 1 diabetes mellitus and coeliac disease. *Clinical Endocrinology.* 88(1) pp.37-43.

Tong, A., Sainsbury, P. & Craig, J. (2007) Consolidated criteria for reporting qualitative research (COREQ): A 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care : Journal of the International Society for Quality in Health Care.* 19(6) pp.349-357.

Tovoli, F., Negrini, G., Sansone, V., Faggiano, C., Catenaro, T., Bolondi, L. & Granito, A. (2018) Celiac disease diagnosed through screening programs in at-risk adults is not associated with worse adherence to the gluten-free diet and might protect from osteopenia/osteoporosis. *Nutrients.* 10(12) pp.1940.

Tripepi, G., Jager, K.J., Dekker, F.W. & Zoccali, C. (2010) Selection bias and information bias in clinical research. *Nephron.Clinical Practice.* 115(2) pp.c94-9.

Troncone, R. & Discepolo, V. (2014) Celiac disease and autoimmunity. *Journal of Pediatric Gastroenterology and Nutrition.* 59 Suppl 1pp.S9-S11.

Turner III, D.W. (2010) Qualitative interview design: A practical guide for novice investigators. *The Qualitative Report.* 15(3) pp.754.

Ukkola, A., Mäki, M., Kurppa, K., Collin, P., Huhtala, H., Kekkonen, L. & Kaukinen, K. (2011) Diet improves perception of health and well-being in symptomatic, but not asymptomatic, patients with celiac disease. *Clinical Gastroenterology and Hepatology.* 9(2) pp.118-123. e1.

Ukkola, A., Maki, M., Kurppa, K., Collin, P., Huhtala, H., Kekkonen, L. & Kaukinen, K. (2012) Changes in body mass index on a gluten-free diet in coeliac disease: A nationwide study. *European Journal of Internal Medicine.* 23(4) pp.384-388.

Vaarala, O., Jokinen, J., Lahdenkari, M. & Leino, T. (2017) Rotavirus vaccination and the risk of celiac disease or type 1 diabetes in finnish children at early life. *The Pediatric Infectious Disease Journal.* 36(7) pp.674-675.

Vader, W., Kooy, Y., van Veelen, P., de Ru, A., Harris, D., Benckhuijsen, W., Drijfhout, J.W. & Koning, F. (2002) The gluten response in children with celiac disease is directed toward multiple gliadin and glutenin peptides. *Gastroenterology.* 122(7) pp.1729-1737.

Vahedi, K., Mascart, F., Mary, J., Laberenne, J., Bouhnik, Y., Morin, M., Ocmant, A., Velly, C., Colombel, J. & Matuchansky, C. (2003) Reliability of antitransglutaminase antibodies as predictors of gluten-free diet compliance in adult celiac disease. *The American Journal of Gastroenterology.* 98(5) pp.1079.

Valenzuela, D. & Shrivastava, P. (2002) Interview as a method for qualitative research. *Southern Cross University and the Southern Cross Institute of Action Research (SCIAR).*

van der Windt, Daniëlle AWM, Jellema, P., Mulder, C.J., Kneepkens, C.F. & van der Horst, Henriëtte E (2010) Diagnostic testing for celiac disease among patients with abdominal symptoms: A systematic review. *Jama.* 303(17) pp.1738-1746.

van der Wouden, E.J., Nelis, G.F. & Vecht, J. (2007) Screening for coeliac disease in patients fulfilling the rome II criteria for irritable bowel syndrome in a secondary care hospital in the netherlands: A prospective observational study. *Gut.* 56(3) pp.444-445.

van Heel, D.A. & West, J. (2006) Recent advances in coeliac disease. *Gut.* 55(7) pp.1037-1046.

van Hees, N.J., Van der Does, W. & Giltay, E.J. (2013) Coeliac disease, diet adherence and depressive symptoms. *Journal of Psychosomatic Research.* 74(2) pp.155-160.

VanGeest, J.B., Wynia, M.K., Cummins, D.S. & Wilson, I.B. (2001) Effects of different monetary incentives on the return rate of a national mail survey of physicians. *Medical Care.* 39(2) pp.197-201.

Vedsted, P. & Christensen, M.B. (2005) Frequent attenders in general practice care: A literature review with special reference to methodological considerations. *Public Health.* 119(2) pp.118-137.

Verma, A.K., Lionetti, E., Gatti, S., Franceschini, E., Catassi, G.N. & Catassi, C. (2018) Contribution of oral hygiene and cosmetics on contamination of gluten-free diet: Do celiac customers need to worry about? *Journal of Pediatric Gastroenterology and Nutrition.*

Verrill, L., Zhang, Y. & Kane, R. (2013) Food label usage and reported difficulty with following a gluten-free diet among individuals in the USA with coeliac disease and those with noncoeliac gluten sensitivity. *Journal of Human Nutrition and Dietetics.* 26(5) pp.479-487.

Vici, G., Belli, L., Biondi, M. & Polzonetti, V. (2016) Gluten free diet and nutrient deficiencies: A review. *Clinical Nutrition.* 35(6) pp.1236-1241.

Viljamaa, M., Collin, P., Huhtala, H., Sievanen, H., Maki, M. & Kaukinen, K. (2005) Is coeliac disease screening in risk groups justified? A fourteen-year follow-up with special focus on compliance and quality of life. *Alimentary Pharmacology & Therapeutics.* 22(4) pp.317-324.

Villafuerte-Galvez, J., Vanga, R., Dennis, M., Hansen, J., Leffler, D., Kelly, C. & Mukherjee, R. (2015) Factors governing long-term adherence to a gluten-free diet in adult patients with coeliac disease. *Alimentary Pharmacology & Therapeutics.* 42(6) pp.753-760.

Villalta, D., Crovatto, M., Stella, S., Tonutti, E., Tozzoli, R. & Bizzaro, N. (2005) False positive reactions for IgA and IgG anti-tissue transglutaminase antibodies in liver cirrhosis are common and method-dependent. *Clinica Chimica Acta.* 356(1-2) pp.102-109.

Villanacci, V. (2015) What is the best histopathological classification for celiac disease? does it matter? A letter of comment to the review of amado salvador pena A new proposal. *Gastroenterology and Hepatology from Bed to Bench.* 8(4) pp.306-308.

Vilppula, A., Kaukinen, K., Luostarinen, L., Krekelä, I., Patrikainen, H., Valve, R., Mäki, M. & Collin, P. (2009) Increasing prevalence and high incidence of celiac disease in elderly people: A population-based study. *BMC Gastroenterology.* 9(1) pp.49.

Vilppula, A., Kaukinen, K., Luostarinen, L., Krekela, I., Patrikainen, H., Valve, R., Luostarinen, M., Laurila, K., Maki, M. & Collin, P. (2011) Clinical benefit of gluten-free diet in screen-detected older celiac disease patients. *BMC Gastroenterology.* 11pp.136-230X-11-136.

Violato, M., Gray, A., Papanicolas, I. & Ouellet, M. (2012) Resource use and costs associated with coeliac disease before and after diagnosis in 3,646 cases: Results of a UK primary care database analysis. *PLoS One.* 7(7) pp.e41308.

Visser, P.S., Krosnick, J.A., Marquette, J. & Curtin, M. (1996) Mail surveys for election forecasting? an evaluation of the columbus dispatch poll. *Public Opinion Quarterly.* 60(2) pp.181-227.

Volta, U., Granito, A., Fiorini, E., Parisi, C., Piscaglia, M., Pappas, G., Muratori, P. & Bianchi, F.B. (2008) Usefulness of antibodies to deamidated gliadin peptides in celiac disease diagnosis and follow-up. *Digestive Diseases and Sciences.* 53(6) pp.1582-1588.

Volta, U., Ravaglia, G., Granito, A., Forti, P., Maioli, F., Petrolini, N., Zoli, M. & Bianchi, F.B. (2001) Coeliac disease in patients with autoimmune thyroiditis. *Digestion.* 64(1) pp.61-65.

Wahab, P., Meijer, J., Goerres, M. & Mulder, C. (2002) Coeliac disease: Changing views on gluten-sensitive enteropathy. *Scandinavian Journal of Gastroenterology.* 37(236) pp.60-65.

Wahnschaffe, U., Ullrich, R., Riecken, E. & Schulzke, J. (2001) Celiac disease–like abnormalities in a subgroup of patients with irritable bowel syndrome. *Gastroenterology.* 121(6) pp.1329-1338.

Walia, B.N., Sidhu, J.K., Tandon, B.N., Ghai, O.P. & Bhargava, S. (1966) Coeliac disease in north indian children. *British Medical Journal.* 2(5524) pp.1233-1234.

Walker, J.L. (2012) Research column. the use of saturation in qualitative research. *Canadian Journal of Cardiovascular Nursing.* 22(2) .

Walker, A.J., Curtis, H.J., Bacon, S., Croker, R. and Goldacre, B., 2018. Trends, geographical variation and factors associated with prescribing of gluten-free foods in English primary care: a cross-sectional study. *BMJ open*, *8*(3), p.e021312.

Walker, E.A., Shmukler, C., Ullman, R., Blanco, E., Scollan-Koliopoulus, M. & Cohen, H.W. (2011) Results of a successful telephonic intervention to improve diabetes control in urban adults: A randomized trial. *Diabetes Care.* 34(1) pp.2-7.

Walker-Smith, J., Guandalini, S., Schmitz, J., Shmerling, D. & Visakorpi, J. (1990) Revised criteria for diagnosis of coeliac disease. *Archives of Disease in Childhood (United Kingdom).*

Walker-Smith, J.A. (1973) Coeliac disease in children of asian immigrants. *Lancet.* 1(7800) pp.428.

Walsh, M. (2003) Teaching qualitative analysis using QSR NVivo. *The Qualitative Report.* 8(2) pp.251-256.

Wandel, M., Råberg, M., Kumar, B. & Holmboe-Ottesen, G. (2008) Changes in food habits after migration among south asians settled in oslo: The effect of demographic, socio-economic and integration factors. *Appetite.* 50(2-3) pp.376-385.

Wasson, J., Gaudette, C., Whaley, F., Sauvigne, A., Baribeau, P. & Welch, H.G. (1992) Telephone care as a substitute for routine clinic follow-up. *Jama.* 267(13) pp.1788-1793.

Watson, R.G. (2005) Diagnosis of coeliac disease. *BMJ (Clinical Research Ed.).* 330(7494) pp.739-740.

WCRF (2013) *Food Diary.* Available at: http://www.wcrf-uk.org/PDFs/Food-diary.pdf . (Accessed: 19 February 2019).

Webb, C., Myléus, A., Norström, F., Hammarroth, S., Högberg, L., Lagerqvist, C., Rosén, A., Sandström, O., Stenhammar, L. & Ivarsson, A. (2015) High adherence to a gluten-free diet in adolescents with screening-detected celiac disease. *Journal of Pediatric Gastroenterology and Nutrition.* 60(1) pp.54-59.

Weile, B., Cavell, B., Nivenius, K. & Krasilnikoff, P.A. (1995) Striking differences in the incidence of childhood celiac disease between denmark and sweden: A plausible explanation. *Journal of Pediatric Gastroenterology and Nutrition.* 21(1) pp.64-68.

Weinberger, M., Tierney, W.M., Cowper, P.A., Katz, B.P. & Booher, P.A. (1993) Cost-effectiveness of increased telephone contact for patients with osteoarthritis: A randomized, controlled trial. *Arthritis & Rheumatology.* 36(2) pp.243-246.

Welander, A., Tjernberg, A.R., Montgomery, S.M., Ludvigsson, J. & Ludvigsson, J.F. (2010) Infectious disease and risk of later celiac disease in childhood. *Pediatrics.* pp.peds. 2009-1200.

Welsh, E. (2002) Dealing with data: Using NVivo in the qualitative data analysis process. In: *Forum Qualitative Sozialforschung/Forum: Qualitative Social Research.*

West, J., Fleming, K.M., Tata, L.J., Card, T.R. & Crooks, C.J. (2014) Incidence and prevalence of celiac disease and dermatitis herpetiformis in the UK over two decades: Population-based study. *The American Journal of Gastroenterology.* 109(5) pp.757-768.

West, J., Logan, R.F., Hill, P.G. & Khaw, K. (2007) The iceberg of celiac disease: What is below the waterline? *Clinical Gastroenterology and Hepatology.* 5(1) pp.59-62.

West, J., Logan, R.F., Smith, C.J., Hubbard, R.B. & Card, T.R. (2004) Malignancy and mortality in people with coeliac disease: Population based cohort study. *BMJ (Clinical Research Ed.).* 329(7468) pp.716-719.

Whitaker, J.K., West, J., Holmes, G.K. & Logan, R.F. (2009) Patient perceptions of the burden of coeliac disease and its treatment in the UK. *Alimentary Pharmacology & Therapeutics.* 29(10) pp.1131-1136.

White, L., Bannerman, E. & Gillett, P. (2016) Coeliac disease and the gluten-free diet: A review of the burdens; factors associated with adherence and impact on health-related quality of life, with specific focus on adolescence. *Journal of Human Nutrition and Dietetics.* 29(5) pp.593-606.

White, L.E., Merrick, V.M., Bannerman, E., Russell, R.K., Basude, D., Henderson, P., Wilson, D.C. & Gillett, P.M. (2013) The rising incidence of celiac disease in scotland. *Pediatrics.* 132(4) pp.e924-31.

Whyte, L.A. & Jenkins, H.R. (2013) The epidemiology of coeliac disease in south wales: A 28-year perspective. *Archives of Disease in Childhood.* 98(6) pp.405-407.

Wierdsma, N.J., van Bokhorst-de van der Schueren, Marian AE, Berkenpas, M., Mulder, C.J. & van Bodegraven, A.A. (2013) Vitamin and mineral deficiencies are highly prevalent in newly diagnosed celiac disease patients. *Nutrients.* 5(10) pp.3975-3992.

Wijmenga, C. & Gutierrez-Achury, J. (2014) Celiac disease genetics: Past, present and future challenges. *Journal of Pediatric Gastroenterology and Nutrition.* 59 Suppl 1pp.S4-7.

Wildman, M.J., Sanderson, C., Groves, J., Reeves, B.C., Ayres, J., Harrison, D., Young, D. & Rowan, K. (2007) Implications of prognostic pessimism in patients with chronic obstructive pulmonary disease (COPD) or asthma admitted to intensive care in the UK within the COPD and asthma outcome study (CAOS): Multicentre observational cohort study. *BMJ (Clinical Research Ed.).* 335(7630) pp.1132.

Wolf, R.L., Green, P.H., Lee, A.R., Reilly, N.R., Zybert, P. and Lebwohl, B., 2019. Benefits From and Barriers to Portable Detection of Gluten, Based on a Randomized Pilot Trial of Patients With Celiac Disease. *Clinical Gastroenterology and Hepatology*.

Wolf, R.L., Lebwohl, B., Lee, A.R., Zybert, P., Reilly, N.R., Cadenhead, J., Amengual, C. & Green, P.H.R. (2018) Hypervigilance to a gluten-free diet and decreased quality of life in teenagers and adults with celiac disease. *Digestive Diseases and Sciences.* 63(6) pp.1438-1448.

Woogara, J. (2005) Patients' rights to privacy and dignity in the NHS. *Nursing Standard (Royal College of Nursing (Great Britain) : 1987).* 19(18) pp.33-37.

Wylie, C., Geldart, S. & Winwood, P. (2005) Dietitian-led coeliac clinic: A successful change in working practice in modern healthcare. *Gastroenterol.Today.* 15pp.11-12.

Xhakollari, V., Canavari, M. and Osman, M., 2018. Factors affecting consumers' adherence to gluten-free diet, a systematic review. *Trends in Food Science & Technology*.

Yachha, S.K., Aggarwal, R., Srinivas, S., Srivastava, A., Somani, S.K. & Itha, S. (2006) Antibody testing in indian children with celiac disease. *Indian Journal of Gastroenterology.* 25(3) pp.132.

Yachha, S.K., Misra, S., Malik, A.K., Nagi, B. & Mehta, S. (1993) Spectrum of malabsorption syndrome in north indian children. *Indian Journal of Gastroenterology : Official Journal of the Indian Society of Gastroenterology.* 12(4) pp.120-125.

Yachha, S.K. & Poddar, U. (2007) Celiac disease in india. *Indian Journal of Gastroenterology : Official Journal of the Indian Society of Gastroenterology.* 26(5) pp.230-237.

Yang, A., Chen, Y., Scherl, E., Neugut, A.I., Bhagat, G. & Green, P.H. (2005) Inflammatory bowel disease in patients with celiac disease. *Inflammatory Bowel Diseases.* 11(6) pp.528-532.

Yang, R., Carter, B.L., Gums, T.H., Gryzlak, B.M., Xu, Y. & Levy, B.T. (2017) Selection bias and subject refusal in a cluster-randomized controlled trial. *BMC Medical Research Methodology.* 17(1) pp.94.

Yel, L. (2010) Selective IgA deficiency. *Journal of Clinical Immunology.* 30(1) pp.10-16.

Young, I. & Thaivalappil, A. (2018) A systematic review and meta-regression of the knowledge, practices, and training of restaurant and food service personnel toward food allergies and celiac disease. *PloS One.* 13(9) pp.e0203496.

Yuan, J., Zhou, C., Gao, J., Li, J., Yu, F., Lu, J., Li, X., Wang, X., Tong, P. & Wu, Z. (2017) Prevalence of celiac disease autoimmunity among adolescents and young adults in china. *Clinical Gastroenterology and Hepatology.*

Zabolotsky, A.H., Sowa, P., Moleski, S., Brandt, D.R., Janowski, R., Yoo, J., Krawitz, S., DiMarino, A. and Voorhees, K.N., 2017. Effects of Patient Education on Adherence and Quality of Life in Celiac Disease at a Tertiary Celiac Center. *Gastroenterology*, *152*(5), p.S746.

Zanchetta, M.B., Longobardi, V. & Bai, J.C. (2016) Bone and celiac disease. *Current Osteoporosis Reports.* 14(2) pp.43-48.

Zanchi, C., Di Leo, G., Ronfani, L., Martelossi, S., Not, T. & Ventura, A. (2008) Bone metabolism in celiac disease. *The Journal of Pediatrics.* 153(2) pp.262-265.

Zanoni, G., Navone, R., Lunardi, C., Tridente, G., Bason, C., Sivori, S., Beri, R., Dolcino, M., Valletta, E. & Corrocher, R. (2006) In celiac disease, a subset of autoantibodies against transglutaminase binds toll-like receptor 4 and induces activation of monocytes. *PLoS Medicine.* 3(9) pp.e358.

Zarkadas, M., Dubois, S., MacIsaac, K., Cantin, I., Rashid, M., Roberts, K., La Vieille, S., Godefroy, S. & Pulido, O. (2013) Living with coeliac disease and a gluten-free diet: A canadian perspective. *Journal of Human Nutrition and Dietetics.* 26(1) pp.10-23.

Zarkadas, M., Cranney, A., Case, S., Molloy, M., Switzer, C., Graham, I., Butzner, J., Rashid, M., Warren, R. & Burrows, V. (2006) The impact of a gluten-free diet on adults with coeliac disease: Results of a national survey. *Journal of Human Nutrition and Dietetics.* 19(1) pp.41-49.

Zelnik, N., Pacht, A., Obeid, R. & Lerner, A. (2004) Range of neurologic disorders in patients with celiac disease. *Pediatrics.* 113(6) pp.1672-1676.

Zevit, N. & Shamir, R. (2014) Diagnosis of celiac disease: Where are we heading after the ESPGHAN 2012 guidelines? *Journal of Pediatric Gastroenterology and Nutrition.* 59 Suppl 1pp.S13-5.

Ziberna, F., De Lorenzo, G., Schiavon, V., Arnoldi, F., Quaglia, S., De Leo, L., Vatta, S., Martelossi, S., Burrone, O. & Ventura, A. (2016) Lack of evidence of rotavirus-dependent molecular mimicry as a trigger of coeliac disease. *Clinical & Experimental Immunology.* 186(3) pp.356-363.

Zipser, R.D., Patel, S., Yahya, K.Z., Baisch, D.W. & Monarch, E. (2003) Presentations of adult celiac disease in a nationwide patient support group. *Digestive Diseases and Sciences.* 48(4) pp.761-764.

Zschocke, I., Mrowietz, U., Karakasili, E. & Reich, K. (2014) Non-adherence and measures to improve adherence in the topical treatment of psoriasis. *Journal of the European Academy of Dermatology and Venereology.* 28pp.4-9.

Zysk, W., Głąbska, D. & Guzek, D. (2018) Social and emotional fears and worries influencing the quality of life of female celiac disease patients following a gluten-free diet. *Nutrients.* 10(10) pp.1414.